

Vitamin C's Variant Effects on Covid-19 Patients

**Maryam sanei¹, Parisa motifard¹, Yalda Askari sadat mahalleh², Saba zaeri¹, Setayesh mostafavi¹, Asal Mohse-
ni¹, Mahsa Mazaheri tirani¹, Sasan heidariesfahani¹ and Hossein Esmaeili^{3,*}**

¹Faculty of Medicine, Medical university of isfahan, Iran

²Faculty of Medicine, Iran university of medical science, Tehran, Iran

³Department of Medicine, Islamic Azad University Tehran Medical Sciences, Tehran, Iran

***Corresponding author:** Hossein Esmaeili, Medical Student, Department of Medicine, Islamic Azad University Teh-
ran Medical Sciences, Tehran, Iran.

Received: April 21, 2022

Published: May 17, 2022

Abstract

The target is to evaluate ascorbic acid effect on prevention or treatment of the most recent viral infection, SARS-CoV-2.

Covid-19 is a Systemic disease that can cause a sharp increase in cytokines, resulting in pulmonary capillary endothelial cell activation. Increasing neutrophil infiltration and oxidative stress. Coronavirus activates macrophages to release molecules such as NO. Vitamin C enhance chemotaxism, migration and decreases ROS release. It also reduces the secretion of cytokines, especially 6-IL and TNF- α .

Vitamin C can help increase the rate of recovery in hospitalization by 70% and quantitative analysis indicated that it may reduce patients' symptoms by 30%. High dose Ascorbic acid infusion causes positive interference in sodium, glucose and creatinine also negative interference in lipase, Triglycerides, direct bilirubin and LDL / HDL cholesterol. Co-treatment of vitamin C with Melatonin, Vitamin D and Zinc can have a synergic effect on treatment. Although; in a study high doses of zinc gluconate and ascorbic acid, had no significant effect on reducing the course of symptoms.

Keywords: Vitamin c; Ascorbic acid; IV Vit C; Covid-19; SARS-CoV-2; Coronavirus.

Introduction

Many experimental studies have been a proof to indicate the boosting effects of vitamin C to the immune system. This essential micronutrient can enhance phagocytosis-induced cell death, chemotaxis, prevent the ROS formation, help proliferation of B- and T-cells and even significantly attenuate the NET formation [1-3].

It is well known that a diet of less than 11.4 daily mg of vitamin C indicates a deficiency [15].

Vitamin C deficiency has been correlated to acute respiratory complications and even sepsis; [4,5] there is no adequate consideration to support its possible effect in reduction or prophylaxis of viral disease incidences when used in high doses [3,5]. However many authors have underlined such effectiveness in interference with common cold or other viral infections [6].

In an analysis of 8 RCTs on children, it was confirmed that vitamin C supplements could significantly reduce the duration of the infection (by 14%) and severity of it but had no apparent effect on the frequency and the incidents of URTI [7].

Infections with SARS-CoV-2 and its development into respiratory failure, increases cytokines such as 6-IL and 1-ET. This cause neutrophils to accumulate in lungs and destroy alveolar capillaries [17].

IV high dose vitamin C therapy has been among the shortlist of potential drug regimens being tested for efficacy in the treat-

ment of covid-19 [8].

Although global vaccination had let to an acceptable immunity; the mutations occurring in the viruses result in frequent emergence of new strains which may give low effectiveness throughout vaccination program duration [9].

Therefore, alternative strategies should always be an in-hand option to combat the pandemics in lack of time. In this review we address that hypothesis examined by multiple scientists whether to trust vitamin C effects on covid-19 like we did on previous viral infections.

Vitamin c can have an effect on overall mortality rate of the patients

According to a study, by every 10 years of increasing age, the risk of death due to Covid-19 increases 2.7 times. In this small pilot study on 21 patients with severe Covid-19 disease (15 men and 6 women, 17 Hispanic and 4 Caucasian) By Mean age of 61 years; in order to evaluate the age and serum level of vitamin C as a predictor of mortality, 11 persons survived (44% of mortality). Older age and low levels of vitamin C are shown as Covid-19-related mortality risk factors in this experiment; by the result of a multivariate regression model for both age and vitamin C as predictors of mortality [10].

In another experiment, the use of oral ascorbic acid therapy in COVID-19 patients had very little effect on reducing over-

all mortality, increasing extubation rate and decreasing ICU mortality rate. Out of 176 patients with the desired criteria, 96 patients were included in the ascorbic acid group; of which 30 patients were in the ICU and 28 patients were intubated, and 80 patients were included in the control group; of which 27 patients were in the ICU and 19 patients were intubated. Mortality was 23% in the ascorbic acid group compared with 33% in the control group, extubation was 78% in the ascorbic acid group compared with 58% in the control group and The ICU mortality rate was 50% in the ascorbic acid group to 59% in the control group [11].

However, in this study, 160 PCR positive volunteers participated and 20% of them received 6 mg of daily vitamin C. According to studies and tests performed, in ICU-deceased patients and patients receiving vitamin C, the NLR rate of which it's raised levels is associated with occurrence of mortality; has been increased. However, at the time of leave, the rate was similar in both case and control groups.

Despite the fact that vitamin C improves the function of the immune system; in this study a positive effect on items such as admission time, ICU mortality rate, factor level of ferritin-dimer, Prolactin intubation and use of HFNC was not seen. Use of steroids, antibacterial and Antiviruses also did not set a positive effect [12].

In a study by Al. Sulaiman and his colleagues, out of 739 patients with inclusion criteria, 158 (21.3%) received ascorbic acid and 581 (78.7%) were in the control group and a total of 296 patients have been added after PSM (propensity score matching) using baseline severity codes (including: APACHE II, SOFA score, NUTRIC score), Systemic use of corticosteroids and study centers. Finally, it was found that the use of ascorbic acid is not associated with a reduction in mortality of hospitalized patients or 30- days ICU mortality and secondary effects of it include increased hospital stay and the use of invasive methods such as mechanical ventilators [13].

In another study on 84 patients with covid-19, including a group of 46 persons receiving high-dose intravenous vitamin C and a group of 30 people for standard therapy to evaluate the effect of vitamin C. 8 persons with special conditions (pregnant, lactating people, Allergic to vitamin C, under 18 years, etc.) Were excluded from the study. The weight of the people is not taken into account. At the end, they found that the risk of mortality due to covid-19 in the group of receiving high-dose vitamin C in compared to the standard therapy decreased significantly. During the first 18 days, a higher percentage of high-dose vitamin C group than the standard therapy group had improvement in oxygen support status, which is one of the reasons for the reduction of deaths due to the disease [14].

Overall effects of vitamin c in prophylaxis and management of covid-19

The investigation and studies show that, most patient with COVID-19 have a significant plasma vitamin c deficiency, therefore use of high dose vitamin c supplement is recommended in treatment of COVID-19. In general, vitamin C deficiency can cause COVID-19 progression and COVID-19 also cause vitamin C deficiency.

According to this study, the highest level of plasma vitamin C is observed in heparin and EDTA [15].

One way to analyze the effect of vitamin C on the recovery rate is to use survival analysis; which affects the patients who have had a recovery process during the follow-up. Hemilä and her team calculated the rate of improvement between vitamin

C and the usual care arms and it was found that vitamin C increases the rate of recovery by 70% and quantitative analysis indicated that it may reduce patients' symptoms by 30% [16].

The Role of Vitamin C as Adjuvant Therapy was examined on patients who received IV VC (intravenous vitamin C) compared to those who received standard treatment, their symptoms improved sooner and fewer days was spent in the hospital. But there was no significant difference in need for mechanical ventilation and mortality rate in this article [17].

And so, the same results obtained by Kumari's team whose assigned 150 COVID-19 patients (75 patients in standard care group plus IV VC intakes and 75 patients receiving only standard care) with faster symptom improvement (SOC + IV VC = 7.1 ± 1.8 vs. SOC without IV VC = 9.6 ± 2.1 days) and lower hospitalization days (SOC + IV VC = 8.1 ± 1.8 vs. SOC without IV VC = 10.7 ± 2.2 days) in comparison to control group. There was no statistically significant difference in age, respiratory rate, CRP and LDH levels among the groups [18].

A related case report also issues the novel opinion of prophylactic and curative effect of Vitamin C daily regular intake via homeostatic and epigenetic mechanisms. The first and second participants whom consumed fixed 100 mg daily or an increased amount, tested COVID negative. But the third and fourth participants whom withdraw the usage in between, even with higher daily dosage uptake, had a Covid-19 positive test indicating the importance of continuous usage. This case also approved that co-treatment of ascorbic acid tablets and hot pulp of vitamin C enriched plants (drank or inhaled) causes a faster recovery [39].

Role of vitamin c as an antioxidant in tretment of Covid-19

Factors that can reduce inflammatory cytokines are useful as COVID-19 treatment. Vitamin C is a powerful antioxidant that lowers cytokines, which in turn reduces inflammation in patients with covid-19 [20].

It also improves symptoms such as sneezing-runny nose and swollen sinuses in covid-19 patients [21].

As an antioxidant, it Reduces free radicals thus controls pneumonia. In addition, in type II pneumocytes, it acts as an antioxidant and protects cells, which maintains the blood-air barrier intact. In immune cells vitamin c acts as a pro-oxidant [22].

In patients with Covid-19, the production of oxygen free radicals increases, which resulting in destruction of the microvascular endothelial layer. By damaging to this layer, serum permeability into the tissue is increased, which eventually leads to organ failure. Vitamin c as an antioxidant can inactivate these free radicals therefore prevent organ failure [14].

It has also shown to reduce the risk of thrombosis by anti-inflammatory activity in critically ill patients of covid-19 in another study [19].

Effect of vitamin c on inflammatory factors and cytokines

Covid-19 is a Systemic disease that can cause a sharp increase in cytokines, resulting in pulmonary capillary endothelial cell activation. Increasing neutrophil infiltration and oxidative stress. Oxidative stress causes severe hypoxia, inflammation and Damage to the air-blood barrier.31 Inflammation and oxidative stress are caused by Interleukin (IL-6) and endothelin (ET-1) in covid-19 disease [24].

During a study in Iran, 73 patients were evaluated (38 patients

in the intervention group and 34 patients in control group). 3 patients in the intervention group (7.89 %) (and 5 Patients in the control group (14.71 %) needed ICU admission. In this experiment, even though they expected an effective role for vitamin C in covid-19 treatment, in clinical study it did not have significant effect compared to the control group. The only difference was lower RR (respiratory rate) in the intervention group compared to the control group. Also, treatment failure was less and the length of hospital stay was shorter in the intervention group, although insignificant. As previously known; neutrophils can result in inflammatory necrosis therefore Vitamin C prevents inflammatory necrosis by reducing the number of neutrophils [20].

In another study on alteration of inflammatory factor during covid-19, 236 patients with COVID-19 who almost have similar clinical symptoms were selected. 85 of them received treatment of HIVC (High-dose intravenous vitamin C) according to a same protocol. Before starting treatment, blood test result of most patients showed a high levels of inflammatory factors hc-CRP / IL-6 / TNF- α and hyperinflammatory state. After 21 days, it was found that inflammatory factors were reduced in almost all patients, but in Patients who received vitamin C injections had a higher reduction rate. In general, HIVC can be effective in improving the hyperinflammatory state patients and reducing the mortality rate [25].

Vitamin C is useful for the treatment of bacterial and viral diseases, but whether high-dose Vitamin C injection is useful or not is under investigation. Vitamin C helps keep neutrophil walls intact, it enhances chemotactism, migration, phagocytosis and decreases ROS release. It also reduces the secretion of cytokines, especially 6-IL and TNF- α [22].

In Turkey Suna Kavurgacı and her colleagues had a study on 361 people with COVID-19, including 153 persons receiving IVC at a dose of 2 mg per day (average for 3 consecutive days) and 170 persons with standard therapy. Patients with high blood pressure, diabetes mellitus, coronary artery disease and chronic obstructive pulmonary disease (COPD) were also included in our study. 37 patients were excluded from the study due to receiving Vitamin D. In addition to IVC, 8 mg daily dexamethasone and favipiravir were administered in doses of 1600 mg twice on the first day and 600 mg twice on the following days for 5 to 10 days. 136 people were recovered from the IVC receiving group and 17 persons died. IVC has had useful effects in treatment of people with severe COVID-19 involvement, but, statistical observations have not shown a significant difference in the rate of inflammatory markers, the need for advanced medical treatment, oxygen support status, and mortality. However, the mean lymphocyte count, CRP and D-dimer decreased. if this treatment does not follow standard protocols, we can see the adverse events of a very high dose of IVC, but since it is rarely observed, we can trust this treatment because there are no adverse event in the standard dose [26].

In another study on patients with covid-19 who received high-dose intravenous vitamin C (case group), Improvement in clinical symptoms was more observed in patients under 60 years old, especially in patients with low oxygen flow, and those with serum hs-CRP level less than 1 mg / l. Although, in general, the difference in the improvement of clinical symptoms in the both groups were not significant. In the case group, serum levels of inflammatory factors hs-CRP, PCT and IL-8 decreased; but serum levels of inflammatory factors IL-2R, IL-6 and TNF- α did not change significantly. Adverse events such as septic-

mia, shock, acute respiratory distress (ARDS), elevated serum creatinine, lymphopenia and Thrombocytopenia was observed in both groups, but was less common in case group [14].

Studies show that thrombosis and clot lysis are regulated by oxidative stress [27].

Increase in oxidative stress-nitrate and nitrite levels in COVID-19 patients compared to healthy individuals has been investigated. Coronavirus activates macrophages to release molecules such as NO, and it has been shown that Inducible Nitric Oxide Synthase (iNos) causes inflammation. Nitric oxide reacts with superoxide and damage cells. Nitric oxide plays an important role in coagulation and organ dysfunction. Nitrite anion oxidizes Hb to Met_Hb which Increases hypoxia, bilirubin and iron level [27].

Effect of vitamin c on para clinical tests

Vitamin c can have effect on different measurements in pre-clinical tests some are as follows:

In a study, 50 positive COVID_19 patients participated (Age of 41-70 years). The recovery rate of co-treatment of vitamin C and dexamethasone was 94%, which is a very acceptable rate. Serum ferritin level which measured by chemiluminescent immunoassays (CLIA) method, in living cases was 478. 81 ng / ml and in dead cases 1410 ng / ml [28].

In another study 17 patients with positive COVID_19 participated who had special conditions such as obesity, old age, high blood pressure and diabetes. Approximately 8 days after the onset of symptoms, these patients were treated with vitamin C for 3 days. The results of paired t-test showed that D_dimer and ferritin levels decreased after treatment with IV VC, also requiring for FiO2 decreased. For the initial treatment of patients, drugs such as IV methylprednisolone (40-125mg), hydroxychloroquine (200mg and 400mg) and tocilizumab (600mg and 800mg) have been used. Need for Intubation did not increase by use of Vitamin C [29].

According to following study Vitamin C could have effect on Measurement of SPO2 and mean body temperature, case and control groups of patients with COVID-19 who did not have a large difference in age; Gender and clinical signs selected. Case group (30 people) received treatment with 1.5g of intravenous vitamin C, every 6 hours for 5 days. After the end of this treatment protocol, on the third day of receiving vitamin C in the case group the mean body temperature was lower and SPO2 was higher than the control group. But on the day of hospital discharge on both groups, mean body temperature decreased and SPO2 increased. In the duration of ICU admission and mortality positive effect was not observed [30].

In another study High dose Ascorbic acid infusion causes positive interference in sodium, glucose (POCT by glucometer) and creatinine also negative interference in lipase, UIBC, Triglycerides, total cholesterol, direct bilirubin and LDL / HDL cholesterol. Besides by increasing Ascorbic acid infusion absolute interference increased [31].

For patients with diabetes, we should pay more attention because by wrong treatment blood glucose level of patient can be dropped as in following study: on 30 patients with 19-COVID who were randomly selected, from each individual 10 ml of blood was taken, next the serum was isolated, divided into 0.5 ml aliquots and ascorbic acid was added.

Eventually, in measurements we observed that RBS in samples with ascorbic acid in compare to blank serum is significantly increased. The presence of ascorbic acid, even in small amounts, because false increment of RBS in measurements,

the reason is as follows:

Ascorbic acid reacts with Hydrogen peroxide due to its antioxidant property after that Hydrogen peroxide is no longer available for RBS measurement testing and the colour change is done incorrectly which causes false hyperglycaemia. So, the patient must be asked if he or she has taken vitamin C before any measurement [40].

Different covid-19 co-treatments with vitamin C

Vitamin c and zinc gluconate

In one study Among 214 patients with a mean age of 45.2 years (SD = 6.14), 132 of whom were female (61.7%), 68 of whom were reported currently or formerly smoking (31.8%) and At least a quarter of them have previously taken vitamins or minerals. Of this number of patients; For 50 patients (23.4%) usual care, 48 patients (22.4%) only ascorbic acid, 58 patients (27.1%) only zinc gluconate and 58 patients (27.1%) were prescribed both supplements. Eventually, the experiment was halted due to low profitability. In the initial results of this test; Patients under routine care, without supplementation had a 50% reduction in symptoms with a mean of 6.7 days (SD = 4.4) that This reduction in symptoms in the other 3 groups is as follows: Patients in the ascorbic acid group were 5.5 days (SD = 3.7), patients in the zinc gluconate group were 5.9 days (SD = 4.9) and patients receiving both supplements in combination were 5.5 days (SD = 3.4). In this study, with ambulatory COVID 19 patients, treatment with high doses of zinc gluconate and ascorbic acid, or a combination of both supplements, had no significant effect on reducing the course of symptoms. There was only a little difference in the secondary outcome of this test, including the days required to stop fever, cough, shortness of breath, and fatigue and in total, before the end of the 28-day study, 17 patients were hospitalized (7.9%) and 3 patients died (1.4%), although the number of hospitalizations and deaths between the 4 groups was not much different. Less than 10% of the population had adverse effects from supplements, most of which were related to gastrointestinal intolerance, including nausea, diarrhea and stomach cramps in the ascorbic acid-receiving group [33].

In another study in India, from 251 COVID-19 patient, 5.2% were in the age group over 60 years, 75.3% were in the age group between 20 to 60 years and the rest were under 20 years. This number included 141 men, 83 women, 12 boys and 15 girls. By the end of the day of the experiment, 245 patients were discharged and 6 patients were treated after this period, which were considered as censored cases. 84.9% of patients were asymptomatic and fever and cough were the predominant symptoms in other patients. The significant differences in survival curves based on gender, age, and travel history, is as follows:

In the survival curve of men, women, girls and boys; the recovery of 92.2% of male patients lasted more than 11 days and the release of 4 males was after the end of the final test day. The recovery of 92.8% of females lasted more than 9 days and 1 female was censored. It took 75% of boys to recover in more than 9 days and 86.7% of girls to recover in more than 10 days, with one girl being censored. In Survival curve based on age; in the age group 0-10 years, the average LS was 11.81 days and in the age group 11-20 years, the average LS was 11.07 days. This average finally reached the highest level in the age group of 81-90 years, which was 16.50 days. Although the mean had

slight fluctuations, but in general, with age, the length of hospital stays in patients increased. In the survival curve based on travel history, 94.7% of patients with travel history, were with LS more than 11 days (2 censored patients), 90.1% of patients with close contact had LS more than 9 days (4 censored patients) and LS of 60% of Patients with no travel history, was more than 13 days. Integrated ZVCKK treatment is effective in reducing the length of hospital stay to about 7 days [34].

Vitamin C and Corticosteroids

Combination treatment effects on length of stay varies from report to report but it can be considered not significant as in a 16-person experiment that studied the effect of corticosteroids and their combination with vitamin C in oxygenation of patients [32].

The duration of mechanical ventilation and the length of hospital stay in ICU were not statistically different between the groups of receiving both vitamin C and Corticosteroids or any of them alone. Daily consumption of dexamethasone reduces mortality in patients who needed oxygen [37,38].

In an experimental group, 11 patients who were taking corticosteroids survived and only 1 out of 5 people who died had been received corticosteroids. However, this study requires a larger group for approval [32].

Vitamin C and Vitamin D

In one study about the worst affected countries by vitamin D deficiency like UK, US, Iran and china Increasing of Inflammatory markers such as ferritin and CRP can be due to their role in suppression of IL-6. In this study no steroid and antiviral used because by suppressing the immune system the can alter the level ferritin and CRP. Using vitamin D instead of expensive antivirals is important and helpful for developing countries [35].

Vitamin C and Mental Health

Corona pandemic also has caused an increase in stress, depression, sleep disorders, fear and sedentary with all these factors being effective in suppressing the immune system and increasing the risk of getting sick. According to a study, exposure to stress for 21 days (CIS) causes Immune system disorders, antioxidant suppression, decreasing GSH / SOD / CAT, increasing MDA and TNF- α / IL-6 / IL-10 cytokines as well as DNA lymphocyte damage. Using Melatonin, Vitamin C and Zinc together cause positive effect on recovery of mentioned signs thus along with other treatment protocols, this treatment can be used [36].

Conclusion

We can conclude that if vitamin C is used according to standard protocols; it can be useful for COVID-19 treatment either in form of oral supplements, Intravenous or combined Vitamin D, zinc or other combinations without any adverse events. Although this is a safe treatment with or without significant positive effect. This paper suggests studies on larger number of patients to evaluate exact effect of vitamin C for treatment against COVID-19.

Abbreviation: AE: Adverse Event; APACHE II score: Acute Physiology And Chronic Health Evaluation Score; ARDS: Acute Respiratory Distress Syndrome; BMI: Body Mass Index; CAT: Plasma Catalase; CIS: Chronic Immobilization Stress; COPD: Chronic Obstructive Pulmonary Disease; COVID-19:

Coronavirus Disease 2019; CRP: C Reactive Protein; EDTA: Ethylenediaminetetraacetic Acid; ET-1: Endothelin₁; FiO₂: The Fraction of Inspired Oxygen; GGO: Ground Glass Opacity; GSH: Glutathione; Hb: Hemoglobin; HFNC: High Flow Nasal Cannula; HP: Hydrogen Peroxide; hs-CRP: High-Sensitivity C-Reactive Protein; ICU: Intensive Care Unit; IL-2R: Interleukin-2 Receptor; IL-6: Interleukin₆; IL-8: Interleukin-8; IQR: Interquartile Range; IV VC: Intravenous Vitamin C; IVC: Intravenous Vitamin C; LDH: Lactate Dehydrogenase; LS: Length of Stay; MDA: Malondialdehyde; NET: Neutrophil Extracellular Trap; NLR: Neutrophil/Lymphocyte Ratio; NO: Nitric Oxide; P value: Probability value; PCT: Procalcitonin; POCT: Point-of-Care Test; PSM: Propensity Score Matching; RBS: Random Blood Sugar; ROS: Reactive Oxygen Species; SD: Standard Deviation; SOC: Standard of Care; SOD: Superoxide Dismutase; SOFA score: Sequential Organ Failure Assessment score; TNF- α : Tumor Necrosis Factor- α ; UIBC: Unsaturated Iron Binding Capacity; URTI: Upper Respiratory Tract Infection; Vit C: Vitamin C; ZVCKK: Zinc-Vitamin C and Kabasura Kudineer

References

- Carr AC, Maggini S. Vitamin C and Immune Function. *Nutrients*, 2017; 9(11): 1211. doi: 10.3390/nu9111211. PMID: 29099763; PMCID: PMC5707683.
- Bozonet SM, Carr AC. The Role of Physiological Vitamin C Concentrations on Key Functions of Neutrophils Isolated from Healthy Individuals. *Nutrients*, 2019; 11(6): 1363. doi: 10.3390/nu11061363. PMID: 31212992; PMCID: PMC6627200.
- Bozonet SM, Carr AC, Pullar JM, Vissers MC. Enhanced human neutrophil vitamin C status, chemotaxis and oxidant generation following dietary supplementation with vitamin C-rich Sun-Gold kiwifruit. *Nutrients*, 2015; 7(4): 2574-2588. doi: 10.3390/nu7042574. PMID: 25912037; PMCID: PMC4425162.
- Chiscano-Camón L, Ruiz-Rodriguez JC, Ruiz-Sanmartin A, Roca O, Ferrer R. Vitamin C levels in patients with SARS-CoV-2-associated acute respiratory distress syndrome. *Crit Care*, 2020; 24(1): 522. doi: 10.1186/s13054-020-03249-y. PMID: 32847620; PMCID: PMC7447967.
- Kilgore D, Najm W. Common respiratory diseases. *Prim Care*, 2010; 37(2): 297-324. doi: 10.1016/j.pop.2010.02.007. PMID: 20493338; PMCID: PMC7119334.
- Cerullo Giuseppe, Negro Massimo, Parimbelli Mauro, Pecoraro Michela, Perna Simone, Liguori Giorgio, et al. The Long History of Vitamin C: From Prevention of the Common Cold to Potential Aid in the Treatment of COVID-19. *Front Immunol*, 2020; 11:574029. doi: 10.3389/fimmu.2020.574029.
- Vorilhon P, Arpajou B, Roussel HV, et al. Retraction Note: Efficacy of vitamin C for the prevention and treatment of upper respiratory tract infection. A meta-analysis in children. *Eur J Clin Pharmacol*, 2021; 77: 941. <https://doi.org/10.1007/s00228-021-03150-9>
- Sanders JM, Monogue ML, Jodlowski TZ, Cutrell JB. Pharmacologic Treatments for Coronavirus Disease 2019 (COVID-19): A Review. *JAMA*, 2020; 323(18): 1824-1836. doi: 10.1001/jama.2020.6019. PMID: 32282022.
- Banerjee D, Kaul D. Combined inhalational and oral supplementation of ascorbic acid may prevent influenza pandemic emergency: a hypothesis. *Nutrition*, 2010; 26(1): 128-132. doi: 10.1016/j.nut.2009.09.015. PMID: 20005468; PMCID: PMC7127226.
- Arvinte Cristian, Maharaj Singh, Paul E Marik. "Serum levels of vitamin C and vitamin D in a cohort of critically ill COVID-19 patients of a North American community hospital intensive care unit in May 2020: a pilot study." *Medicine in drug discovery*, 2020; 8: 100064.
- Patel Manishkumar, et al. "The Significance of Oral Ascorbic Acid in Patients with Covid-19." *Chest*, 2020; 158(4): A325.
- Ozgunay, Seyda Efsun, et al. "The use of vitamin C in the intensive care unit during the COVID-19 pandemic." *The European Research Journal*, 2021; 7(4): 425-431.
- Al Sulaiman, Khalid, et al. "Adjunctive therapy with ascorbic in critically ill patients with COVID-19: A multicenter propensity score matched study.", 2021.
- Gao Dengfeng, et al. "The efficiency and safety of high-dose vitamin C in patients with COVID-19: A retrospective cohort study." *Aging (Albany NY)*, 2021; 13(5): 7020.
- Xing Yaru, et al. "Vitamin C supplementation is necessary for patients with coronavirus disease: An ultra-high-performance liquid chromatography-tandem mass spectrometry finding." *Journal of pharmaceutical and biomedical analysis*, 2021; 196: 113927.
- Hemilä Harri, Anitra C Carr, Elizabeth Chalker. "Vitamin C may increase the recovery rate of outpatient cases of SARS-CoV-2 infection by 70%: reanalysis of the COVID A to Z Randomized Clinical Trial." *Frontiers in immunology*, 2021; 12: 1628.
- Muacevic, A., et al. "The Role of Vitamin C as Adjuvant Therapy in COVID-19.", *Cureus*, 2021; 12(11).
- Kumari, Poona, et al. "The role of vitamin C as adjuvant therapy in COVID-19.", *Cureus* 2020; 12(11).
- Hakamifard Atousa, et al. "The effect of vitamin E and vitamin C in patients with COVID-19 pneumonia; a randomized controlled clinical trial", 2021.
- Junejo Shizma, Mehreen Lateef, Eme Paul Eze. "Immune System Enriching Micronutrients: Essential Ingredient for Wellbeing in COVID-19." *Life and Science 1. supplement*, 2020: 4(4).
- Earar, Kamel, et al. "Biochemical effects and therapeutic application of vitamin C (C₆H₈O₆) on COVID-19 infection." *Revista de Chimie*, 2020; 71(5): 473-478.
- Cheng, Richard Z. "Can early and high intravenous dose of vitamin C prevent and treat coronavirus disease 2019 (COVID-19)?" *Medicine in drug discovery*; 2020; 5: 100028.
- Feyaerts Adam F, Walter Luyten. "Vitamin C as prophylaxis and adjunctive medical treatment for COVID-19?" *Nutrition*, 2020; 79: 110948.
- Xia Guozhi, et al. "High-dose intravenous vitamin C attenuates hyperinflammation in severe coronavirus disease 2019." *Nutrition*, 2021; 91: 111405.
- Suna Kavurgaci, et al. "Effect of high-dose intravenous vitamin C on prognosis in patients with SARS-CoV-2 pneumonia." *Medicina Clinica*, 2021.
- Moghaddam, Ahmad Bagheri, et al. "Application of Methylene Blue-Vitamin CN-acetyl Cysteine for Treatment of Critically Ill COVID-19 Patients, Preliminary Report of a Phase-I Clinical Trial." *Authorea Preprints*, 2020.
- Burugu, Hemanth Reddy, et al. "Activities of serum ferritin and treatment outcomes among COVID-19 patients treated with vitamin C and dexamethasone: an uncontrolled single-center observational study." *Cureus*, 2020; 12(11).
- Hiedra Raul, et al. "The use of IV vitamin C for patients with COVID-19: a case series." *Expert Review of Anti-infective Therapy*, 2020; 18(12): 1259-1261.
- Jamali MoghadamSiahkali, Saeidreza, et al. "Safety and effectiveness of high-dose vitamin C in patients with COVID-19: a randomized open-label clinical trial." *European journal of medical research*, 2021; 26(1): 1-9.
- Yesildal Fatih, Ferruh Kemal Isman. "High dose ascorbic acid treatment in COVID-19 patients raised some problems in clinical chemistry testing." *Turkish Journal of Biochemistry*, 2020; 45(5): 491-498.
- Anstey Matthew, et al. "Vitamin C and corticosteroids in viral pneumonia: A prospective cohort study.", 2020.
- Thomas Suma, et al. "Effect of high-dose zinc and ascorbic acid supplementation vs usual care on symptom length and reduction among ambulatory patients with SARS-CoV-2 infection: the COVID A to Z randomized clinical trial." *JAMA network open*, 2021; 4(2); e210369-e210369.
- Jamuna D, et al. "Survival analysis to assess the length of stay of novel coronavirus (COVID-19) patients under Integrated Medicine-Zinc, Vitamin C & Kabasura Kudineer (ZVcKK)." *European Journal of Molecular & Clinical Medicine*, 2021; 7(10); 1375-1387.
- Waheed, Shahan, et al. "Vitamin D (Cholecalciferol) with Low Dose Vitamin C as a Safe and Effective Therapeutic Modality in an Adult with COVID-19 Pneumonia." *Jepsp-Journal of the College of Physicians and Surgeons Pakistan*, 2021: S90-S92.
- Fatima, Sabiha, et al. "Possible Prophylactic Approach for

-
- SARS-CoV-2 Infection by Combination of Melatonin, Vitamin C and Zinc in Animals." *Frontiers in Veterinary Science*, 2020; 7: 994.
36. Group, The RECOVERY Collaborative. "Dexamethasone in hospitalized patients with Covid-19-preliminary report." *The New England journal of medicine*, 2020.
 37. Jeronimo, Christiane Maria Prado, et al. "Methylprednisolone as adjunctive therapy for patients hospitalized with COVID-19 (Metcovid): a randomised, double-blind, phase IIb, placebo-controlled trial" 2020.
 38. Ohanube, G. A., Uchejeso M. Obeta, and Chinaza R. Ikeagwulonu. "Case reports in the use of vitamin C based regimen in prophylaxis and management of COVID-19 among Nigerians." *J Curr Biomed Rep*, 2020; 1(2): 77-80.
 39. Al-Obaidi, Zaid Mahdi Jaber, et al. "The influence of vitamin-C intake on blood glucose measurements in COVID-19 pandemic." *The Journal of Infection in Developing Countries*, 2021; 15(02): 209-213.
-