

Common anti-oxidant vitamin C as an anti-infective agent with remedial role on SARS-CoV-2 infection. An update

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Abstract

Coronavirus disease -2019 (COVID-19) has led to a world-wide multifaceted crisis. The medical world agonizes to contend with the problem, but a string of tested medications has been proven unavailing. Vitamin C is well described as a salutary antioxidant and some trials conclude that it may be a potential antiviral drug. In high doses, vitamin C can alternate crucial steps in the pathogenesis of sepsis and acute respiratory distress syndrome. This dynamic was the driving force behind trials around the world that tried immunonutrition as a weapon against clinical entities. We summarize the mechanisms of action of vitamin C and its role against infections and the current literature referring to the

potential role of vitamin C in SARS-CoV-2 infection, also as a contingent treatment agent.

Introduction

While COVID-19, a pandemic caused by SARS-CoV-2 [1], is spreading throughout the world, humanity is struggling to confront an intractable situation. The effort to discover a coronavirus-specific medication has drawn into a blind alley and among all tested treatments mostly corticosteroids seem to be salubrious for patients, additionally to standard care [2]. Meanwhile, the vaccination process is slow-burning, despite the promising published results [3,4]. Thus, there is an urgent need to approach new prospects pertaining to possible treatments.

This review is setting out to surface the use of ascorbic acid, a much-debated antioxidant substance, to counter some nodal COVID-19 pathophysiologic procedures. These procedures, including micro-thrombosis, cytokine storm and -au contraire-immunoparalysis, are described in terms of causing pneumonia, ARDS, sepsis and tissue damage, leading to ICU transmission and need for mechanical ventilation. Another important pathway includes macrophage hyperactivation, leading to hyperinflammatory response and nitric oxide increase. Along with the oxidative stress caused due to the severity of the disease, NO is oxidized to toxic metabolites, iron contained in hemoglobin is oxidized from the ferrous to the ferric form, leading to methemoglobinemia, and CRP and LDH are increased. That leads to oxidant-antioxidant imbalance and hypoxia [5-7]. Patients with COVID-19 pneumonia, hypoxia and ARDS have a very low P/F index. Hence, they are in great need of high FiO₂ levels and possible mechanical ventilation respiratory support [8-10]. Furthermore, we report the multiple physiologic pathways in which vitamin C takes place, such as oxidant balance and immune response. Also, we ratiocinate why immunonutrition and specifically vitamin C has been tried for the treatment of many diseases, such as common cold, sepsis and cancer, detailing some promising results. Finally, we dissect the results of the most relevant clinical trials that show a benefit in using high dose intravenous vitamin C against COVID-19 complications and try to infer its optimal position in everyday clinical practice.

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Methods

We conducted a PubMed search using the terms SARS-CoV-2 infection and/or COVID-19 and vitamin C to identify all relevant publications. All type of the identified published articles and their references were searched for additional related articles. Only English written articles were finally included.

Results

The major studies referring to COVID-19 and Vitamin C are presented in Table 1. The general outcome of the studies about VC therapies is that it is safe [11] and efficient at some points. The most hopeful results are the great survival percentage when used as last option [7] and a very high recovery rate presented by Burugu *et al.* [12]. Additionally, the researchers have described an improvement on SpO₂ [11], body temperature [10,11], symptomatic-free days, in-hospital days, total bilirubin, IL-6 plasma levels [13], SOFA score, P/F ratio [10, 13], ferritin plasma levels [9,12], CRP, CD-4 count, LDH [13], D-dimers [9,10] met-Hb and NO toxic metabolites after HDIVC administration [7]. On the other hand some studies did not show specific benefits after usage of vitamin c [14]. The aforementioned results are important because they are pertinent with the findings that VC plasma levels in COVID-19 patients are decreased or undetectable [15-17] and oxidant status is altered [17].

Discussion

Vitamin C: mechanisms of action and immunomodulatory effects

Vitamin C (VC) is well described as a great water-soluble compound, which resides in plasma and cells [18], participating in many crucial physiologic functions in the human body [19,20]. Vitamin C acts as a co-factor for the biosynthesis of norepinephrine, cortisol and carnitine and plays a key role in collagen hydroxylation and synthesis by osteoblasts, hypoxia induced factor (HIF) hydroxylation and regulation, vasopressin and cholecystokinin activity regulation, tyrosine metabolism and histone de-methylation [21-23]. Some additional properties, which are in reviewer's concern, are VC's antioxidant activity and its entrenchment to several anti-inflammatory and immunological proceedings [21]. As an antioxidant, ascorbic acid scavenges free radicals and oxidant products actualized via increasing nitric oxide (NO) by recycling tetrahydrobiopterin, suppressing NADPH oxidase and enhancing NO synthase (NOS) activity and, at a manifold concentration, superoxide dismutase activity to inactivate superoxide, which otherwise blocks NO [24,25]. VC can also regenerate glutathione, α -tocopherol, urate and β -carotene [26]. Consequently, it prevents reactive nitrogen species production, leading to vessel relaxation and improving sepsis-induced decrease of capillary blood flow [27,28]. Additionally, ascorbic acid protects from DNA, lipids and proteins oxidation [26]. Thus, VC is influential in protection against diseases caused by oxidative stress [19].

Vitamin C has also a role in altering inflammatory response and modulating the immune system, which can be described by the term "immunonutrition". There is a lot of discussion about the role of some nutrients in medical daily practice but herein we present the evidence of VC capability of shifting some pathophysiologic tracts. First of all, VC is effective on innate immune system by reinforcing the maintenance of the alveolar epithelial barrier, affecting lipid synthesis and regulating the alveolar fluid clearance by potentiating cystic fibrosis trans-membrane conductance regulator (CFTR) and epithelial sodium channel (ENaC) as shown in mice models [29,30]. Interestingly, VC can regulate polymorphonuclears (PMN) motility and phagocytosis, chemotaxis and T-cell maturation and development additionally to an increase in

lymphoproliferative capacity [21,22,31] as shown in some guinea pig experiments [32]. It is also proved that VC can decrease leukocyte fragility in guinea pig models [33]. Ascorbic acid's effect on chemotaxis may result from detoxifying histamine *in vivo* and decreasing histamine levels [34 35]. Furthermore, it is of great interest that VC is contributing to regulate NETosis [36]. Neutrophil endothelial traps (NETs) is a mechanism to kill pathogens, though they can cause endothelial damage and they are a core pathogenetic mechanism in sepsis-related multiple organ failure [37]. Another major VC potentially beneficial aspect is its ability to regulate the immune balance. According to a study on healthy volunteers, 1g/d VC for 75 days increased IgA, IgM and C3 levels [38]. Experiments in mice have demonstrated that VC can attenuate pro-inflammatory cytokines such as GM-CSF and NF κ B, regulating their pathways maybe due to reactive oxygen species (ROS) suppression, with potential effect on IL-5 reduction. Ascorbic acid can also baste immunosuppressive factors, such as TGF- β , IL-10 and CTLA-4 [29,39-42]. This happens basically due to dose-dependent VC blockage on TNF- α -induced NF κ B activation and agrees with a study that showed decreased cytokine activity in cancer patients after intravenous VC administration [43,44]. VC can encounter as well micro-vascular thrombosis caused by cytokine activation of coagulase cascade during sepsis [29,42]. Last but not least, VC could confront IL-7 mediated ACE2 increase [45] and endothelin-induced IL-6 increase [46].

Vitamin C dosage

Plasma level of Vitamin C below 11 μ mol/L is considered a deficiency, between 11-23 or 28 μ mol/L is marginal and is characterized as hypovitaminosis while the optimal level is equal to or above 50 μ mol/L, which is rarely observed in COVID-19 patients [47-51]. Based on randomized trials, the optimal way of administration is every 6 hours, which can produce steady plasma levels quickly, correct plasma deficiency, normalize neutrophil ascorbic acid levels, provide an appropriate dosing schedule and maintain normal values [52,53], even in septic patients who turn out to have hypovitaminosis or deficiency despite attempts of standard nutrition. Another RCT [54] demonstrates that 2g/d can normalize plasma levels and 10g/d can achieve supranormal levels. Doses below 1g/d orally or 200mg/kg/d parenterally did not cause any adverse effects [52,54,55].

Vitamin C against infections

Based on its biology and profitable effects on the human body, Vitamin C has been tried for the prevention and treatment of viral infections and the discussion about the possible benefits is long-lasting. One of the first hopeful prospects was the use of Vitamin C against common cold to reduce incidence, duration and severity of symptoms. Some RCTs [56-58] used oral daily doses (50-150 mg for 5 years, 1g for 8-16 weeks) and agreed on reduced incidence and severity but disagreed on the effect on the duration of symptoms. Other trials [59,60] used high oral doses (3g/d) to treat common cold and flu but the results were polar opposite. A meta-analysis [61] suggests that VC dosage \geq 2g/d reduces cold duration by 8%, reduces the severity of symptoms and lowers the prevalence in high-risk populations, but not in the general population. In favor of VC antiviral activity were also some studies that used it orally combined with other antioxidants or alone to treat HSV, HIV or EBV and according to the results observed, they proposed a potential impact on viral replication [62-64].

Another possible role of VC is the usage in treating critically ill patients with sepsis, septic shock, ARDS and patients in need of

Table 1. Studies referring to vitamin C and COVID-19.

Study title	Author	Publication date	Study type	Intervention	Main outcomes
Effect of high-dose zinc and ascorbic acid supplementation <i>vs</i> usual care on symptom length and reduction among ambulatory patients with SARS-CoV-2 infection: The COVID A to Z randomized clinical trial	Suma Thomas <i>et al.</i> [14]	February 12, 2021	Randomized Controlled Trial (RCT)	Comparison between 6g VC, Zinc, both and control group in outpatients	No significant primary or secondary outcomes achieved (symptoms, hospitalization, deaths reduction)
Safety and effectiveness of high-dose vitamin C in patients with COVID-19: a randomized open-label clinical trial	Jamali Moghadam Siahkali <i>et al.</i> [11]	February 11, 2021	Randomized Controlled Trial (RCT) plus HCQ	Addition of 6g/d to Lopinavir/Ritonavir no adverse effects	Improvement on day 3 SpO ₂ and body temperature,
The Role of Vitamin C as Adjuvant Therapy in COVID-19	Kumari <i>et al.</i> [13]	November 30, 2020	Randomized Controlled Trial (RCT)	Addition of 50mg/kg/d VC to standard therapy	Improvement on symptomatic-free days (7.1+/- 1.8 <i>vs</i> 9.6+/- 2.1) and days in hospital (8.1+/-1.8 <i>vs</i> 10.7+/-2.2)
Pilot trial of high-dose vitamin C in critically ill COVID-19 patients	Zhang <i>et al.</i> [8]	January 9, 2021	Pilot trial	12g/d IVC	Improvement on SOFA score, total bilirubin, IL-6 and P/F ratio
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	Arvinte <i>et al.</i> [15]	December 8, 2020	Pilot study		VC plasma levels are reduced in critically ill COVID-19 patients
Vitamin C levels in patients with SARS-CoV-2-associated acute respiratory distress syndrome	Chiscano-Camón <i>et al.</i> [16]	August 26, 2020	Prospective cohort study		17 of 18 COVID-19 patients included had undetectable VC plasma levels and 1 of 18 patients had low VC plasma levels
Oxidative stress status in COVID-19 patients hospitalized in intensive care unit for severe pneumonia	Pincemail [17]	February 7, 2021	Pilot study		VC was low and oxidative stress status was altered
Application of methylene blue -vitamin C -N-acetyl cysteine for treatment of critically ill COVID-19 patients	Alamdari <i>et al.</i> [7]	October 15, 2020	Report of phase-I clinical trial	VC 1500 mg/kg/d plus methylene-blue plus N-acetylcysteine	Reduction of methemoglobinemia, NO toxic metabolites, survival of 4 of 5 patients who received MCN as last option
Activities of serum ferritin and treatment outcomes among COVID-19 patients treated with vitamin C and dexamethasone	Burugu <i>et al.</i> [12]	November 11, 2020	Uncontrolled Single-Center Observational Study	VC plus dexamethasone	94% recovery rate, ferritin reduction
Beneficial aspects of high dose intravenous vitamin C on patients with COVID-19 pneumonia in severe condition	Zhao <i>et al.</i> [10]	November 17, 2020	Retrospective case series study	HDIVC (median 162,7 mg/kg to severe, median 178,6mg/kg to critical patients)	Improvement on CRP, temperature, CD4+ count cells, P/F ratio, D-dimers, LDH, SOFA score
The use of IV vitamin C for patients with COVID-19	Hiedra <i>et al.</i> [9]	May 15, 2020	Case-series	VC 1g tid, plus methylprednisolone-HCQ-tocilizumab	Reduction of ferritin and D-dimers

mechanical ventilation. These patients are found to have deficiency or hypovitaminosis C and in ICU patients VC supply is insufficient but high dosage intravenous Vitamin C (HDIVC) can fix plasma levels [52,65,66]. Patients with low VC in plasma tend to have more increased CRP but HDIVC administration could reduce CRP, procalcitonin and SOFA score. One RCT [67] examined the enteral administration of eicosapentaenoic acid plus γ -linoleic acid plus antioxidants including VC against standard diet in patients with severe sepsis and shock in need of mechanical ventilation and resulted in an improvement on oxygenation status, ventilation-free days, ICU-free days, less organ dysfunctions, and decreased mortality rates. Two RCTs [68,69] used VC 1.5g every 6 hours plus thiamine plus hydrocortisone IV, one of them combined them with standard treatment vs standard treatment alone for sepsis and septic shock and the other compared them to hydrocortisone alone to treat sepsis. None of them achieved primary outcomes. The first showed an improvement on vasopressor administration duration and lactate clearance but failed to achieve its primary outcome, in-hospital mortality and all the other secondary outcomes including SOFA score improvement. The second one also failed to achieve its primary outcomes, vasopressor-free days and time alive but resulted on an improved day-3 SOFA score. An additional RCT [52], which used a combination of parenteral antioxidants, including 1g/d bolus, in patients with septic shock, achieved to change hemodynamic parameters and established that VC and vitamin E could have synergistic action. VC could also augment quercetin antioxidant and antiviral properties and may have synergistic action with glycyrrhizic acid [70,71]. Combinations containing selenium and ascorbic acid, preferably parenteral, may be associated with decreased mortality in critically ill patients [39]. CITRIS-ALI [72] was a RCT in which HDIVC (50mg/kg) every 6 hours for 96 hours was administered to ICU-patients with sepsis and ARDS within the first 24 hours since sepsis and ARDS onset. Control group received placebo. In spite of not achieving any primary outcome (SOFA, CRP and thrombomodulin as indexes of organ failure, inflammation and vascular injury), this trial rendered some promising results. 28-day mortality was 29.8% in VC group and 46.3% in placebo group, ventilation-free days were 13.1 vs 10.6, ICU-free days at day 28 were 10.7 vs 7.7 and hospital-free days at day 60 were 22.6 vs 15.5. Meta-analyses on this subject have been also designed. Enteral immunonutrition for ARDS is not supported [73,74] but VC can reduce mortality and vasopressor use duration in patients with sepsis [75]. What is more, two meta-analyses by Hemila described that VC can reduce 7.8% the ICU-stay and by 14% the needed mechanical ventilation. Benefit seems to be proportionate to ventilation time needed, severity of the disease and ICU time spent. No difference was found between enteral and parenteral administration [76,77].

Vitamin C and COVID-19

Vitamin C has been found to be low or undetectable in critically ill patients with COVID-19 associated ARDS in ICU patients and along with age are co-dependent factors for mortality [15-17]. It is also noteworthy the effects of VC on COVID-19 co-morbidities (protective role in pathogenesis of cardio-vascular disease, reducing inflammatory and metabolic markers of hypertensive and diabetic obese patients, kidney protecting, anti-cancer properties) [78-80]. Numerous studies on COVID-19 patients are on the way and some of them have already provided hopeful results, largely arising from VC's influence on disease markers such as bilirubin, d-dimers, C-reactive protein (CRP), ferritin, lactate dehydrogenase (LDH), also on PO_2/FiO_2 (P/F) index and Sequential Organ Failure Assessment (SOFA) score. HDIVC (11 g/d) availed a 74-year-old

woman with ARDS in mechanical ventilation days and ICU stay compared to other patients in the same setting [81], while a 77-year-old woman with ARDS had a rapid worsening after lowering the dose of VC from 6 g twice daily to 1g once daily IV [82]. In a case series, 6 critically ill patients were treated with a mean 178.6 mg/kg/d dose and 6 severe ill patients with a mean 162.7 mg/kg/d dose VC as rescue therapy on aggravation of symptoms of pneumonia and an improvement on inflammatory response (decreased CRP, temperature), immune response (increased CD4+ cells) and organ function (decreased P/F ratio, d-dimers, LDH and SOFA score) were observed [10]. In another case series a statistically insignificant decrease on oxygen requirement and a statistically significant decrease in ferritin and d-dimers were observed in 17 patients on mechanical ventilation when treated with 1 g IVC every 8 h for 3 days [9]. An uncontrolled observational study used dexamethasone and VC combination to treat COVID-19 in-hospital patients and noticed a remarkably high recovery rate of 94%. This study screened patients' ferritin as an index of macrophage activity-related cytokine storm. The mean serum ferritin levels among recovered and expired patients were 478.81 ng/ml and 1410 ng/ml, respectively, suggesting that ferritin could be a prognostic marker of the response to HDIVC [12]. The report of a phase-I clinical trial suggests that VC of a dosage 1500 mg/kg/d combined with N-acetyl-cysteine and methylene-blue (MCN) can improve CRP and LDH serum values and may reduce NO toxic metabolites, methemoglobin and oxidative stress in critically ill COVID-19 patients. This trial used MCN as rescue therapy for 5 patients and 4 of them survived [7]. A RCT compared standard therapy plus 50 mg/kg/d IVC and standard therapy alone. There was statistically significant difference in symptomatic-free days (7.1 ± 1.8 vs 9.6 ± 2.1 days) and in-hospital days (8.1 ± 1.8 vs 10.7 ± 2.2 days) between VC group and control group but there was not statistically significant benefit in %-needed mechanical ventilation (16 vs 20%) and mortality (9.3 vs 14.6%) [14]. A multi-center pilot RCT compared HDIVC group (12g twice a day for 7 days) with a placebo group of COVID-19 ARDS ICU patients. The primary outcome was invasive mechanical ventilation free days at day 28 and was not achieved (26.0 vs 22.0 days). 28-day mortality and ICU mortality were reduced in more severe patients. Total bilirubin was better in HDIVC group at day 3 (8.4 vs 14.9 $\mu\text{mol/L}$). The median SOFA score was improved (from 3.5 to 3) in the HDIVC group and worsened (2 to 6) in the control group on day 7. During the treatment period, P/F was 228.5 mmHg in the HDIVC group and 150.7 mmHg in the control group. IL-6 levels were also improved [8]. An open label RCT compared lopinavir/ritonavir plus hydroxychloroquine plus VC (6 g/d) to lopinavir/ritonavir plus hydroxychloroquine alone. The administration was proven safe, but the only significant outcomes were an improvement on SpO_2 at day 3 since admission and a lower day-3 temperature for the VC group [11]. The effect of VC (8 g) on reducing COVID-19 symptoms was examined by another RCT, which found no significant improvement on symptoms of VC group [14].

There are only a few case reports of major adverse effects after HDIVC, describing acute oxalate nephropathy [83] and acute kidney injury (AKI) with acute tubular injury (ATI) noted in biopsy of two patients [84]. Inferentially, HDIVC is safe and cost-effective at least as rescue therapy.

Based on above, some consensuses have already established protocols for the position of VC in everyday clinical practice. MATH+ protocol suggests that methylprednisolone, ascorbic acid, thiamine and heparin should be administered as soon as possible since oxygen supplementation is needed to avoid ICU transmission [85]. Two other protocols suggest that patients should be screened

for nutritional deficits since their admission to hospital to receive early nutritional support that consists of multiple vitamins, including VC, due to their anti-inflammatory and antioxidant related benefits [51,86]. A Chinese consensus proposes that mild COVID-19 symptoms should be treated with HDIVC (50-100 mg/kg/d) to improve P/F ratio and prevent cytokine storm [87]. UK Chelsea and Westminster hospital ICU stratification and treatment protocol contains anticoagulants plus 1g twice a day enteral or IV Vitamin C since admission [88].

Conclusions

Early nutritional support seems to be an augmented factor for better outcomes in COVID-19 and vitamin C can offer a strong alternative. HDIVC is well tolerated and apparently has a positive expectation, even though some studies failed to provide incontrovertible evidence for its use by achieving their primary outcomes. VC's position can be ubiquitous as it is cost effective and seems to improve the disease's parameters. Protocols introducing the idea of estimating VC deficit should be the springboard for RCTs to identify whether a COVID-19 patient with optimal VC levels could profit from an early administration and whether he could be rescued with HDIVC. The level of VC benefit on the management of COVID-19 is still to be estimated but in our point of view, the incorporation of HDIVC in hospital protocols for critically ill patients can be immediate. Results from ongoing trials will provide more information about its safety, possible clinical outcomes and new prospects such as the combination of VC with other antimicrobial substances.

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