Review Article

Plausibility and Feasibility of Intravenous High-Dose Vitamin C in Long COVID Related Fatigue

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ABSTRACT

A growing body of study evidence on Long COVID syndrome reveals that, in addition to respiratory, olfactory, and gustatory disturbances, further main problems are neuro-psychiatric symptoms such as cognitive dysfunction, sleep disorder, and depression, as well as long-lasting fatigue. However, effective treatment options of fatigue in general are still very rare.

In this review, we explore the plausibility and feasibility of high-dose intravenous (IV) vitamin C in Long COVID related fatigue by referring to our recently published review on nine clinical studies with IV vitamin C for treatment of fatigue due to various diseases and by updating it with regard to three presumable key triggers in the pathophysiology of Long COVID: Psycho-social stress, disturbed neurotransmitter metabolism (e.g. excitotoxicity), and development of auto-antibodies. It is concluded that high-dose IV vitamin C might be a suitable treatment option also for Long COVID related fatigue due to its well-known antioxidant, anti-inflammatory, endothelial-restoring, and immunomodulatory effects.

Key words: Ascorbic acid; Fatigue; Cognitive dysfunction; Sleep disorders; Depression

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INTRODUCTION

It is now well-known that SARS-CoV-2 can not only threaten people's health during the acute infection (COVID-19) but also often results in post-infection symptoms which are summarised under the term Long COVID syndrome [1]. The pathophysiology of COVID-19 is characterised by inflammation and oxidative stress leading to vascular and organ damage and to suppression of adaptive immune responses [2]. This might apply to the post-acute recovery phase as well. The aim of this narrative review is to determine the plausibility and feasibility of high-dose IV vitamin C in Long COVID with a focus on fatigue, a symptom for which effective treatment options are still lacking.

VITAMIN C: SOME KEY FACTS

The term "vitamin C" includes the terms "ascorbic acid" and "ascorbate". The latter is the biologically active form that is oxidised to dehydroascorbate when reactive oxygen species are neutralized. Vitamin C is one of the most effective physiological antioxidants. As an enzymatic co-factor, it is particularly important for the synthesis of collagen and carnitine, the bioavailability of tetrahydrobiopterin, and thus the formation of serotonin, dopamine and nitric oxide (NO), the synthesis of noradrenaline, the biosynthesis of amidated peptides, the degradation of the transcription factor HIF-1 α, and the hypomethylation of DNA [3]. Fatigue, pain, cognitive disorders, and depression-like symptoms are known symptoms of vitamin C deficiency [4].

Various infections are known to be associated with high consumption of vitamin C. Deficiencies in acute infections are frequent [3], also for patients with pneumonia or COVID-19 [5-9]. So far, post-COVID-19 vitamin C plasma levels have not been evaluated. However, a deficiency is most likely since the post-acute recovery phase is also accompanied by oxidative stress and inflammation there by consuming antioxidants. Therefore, it is clinically plausible that substitution of vitamin C in this situation could alleviate fatigue and neuro-psychiatric symptoms by neuro-protective and vasoprotective effects due to its antioxidant and anti-inflammatory properties.

The present review focuses on high-dose IV vitamin C because, in contrast to oral application, only the IV route results in pharmacological plasma levels (>220 μM) [10,11]. Also, most clinical studies with oral vitamin C substitution are qualitatively weak because vitamin C blood levels were not determined; therefore, bioavailability and compliance were not verified. In contrast, IV administration has not only the advantage of 100% bioavailability and compliance, but the high plasma levels reached also offer the advantage of rapid bioavailability in the tissues [12]. Furthermore, also the circumvention of genetically terminated resorption differences is facilitated, which are described e.g. for the vitamin C transporter in patients with COVID-19 [13].

INFUSION OF VITAMIN C IN COVID-19

Until now, the supportive use of vitamin C infusions in COVID-19 has been investigated within 4 controlled studies, showing improved oxygenation, reduction of cytokine storm, faster recovery rate resulting in less hospital days, lower mortality, and risk reduction for severe courses in hospitalised patients [14-17]. The rationale for IV vitamin C in COVID-19 is its immune-modulating properties: It strengthens the viral defence against infection and protects against excessive inflammation (cytokine storm) and oxidative stress [18].

LONG COVID SYNDROME

A recent systematic review and meta-analysis report identified more than 50 long-term effects of COVID 19. The most common were fatigue, anosmia, pulmonary dysfunction, abnormal chest XRay/CT, and neurological disorders [19]. Laboratory markers reported to be elevated were D-dimer, NT-proBNP, C-reactive protein, serum ferritin, procalcitonin, and IL-6, implying involvement in circulatory disorders, cardiac insufficiency and inflammatory reactions. One of the first studies looking at Long COVID was from Wuhan, investigating 1733 patients hospitalised for COVID-19 [19]. Six months later, 63% of those who had recovered still suffered from fatigue or muscle weakness, 26% from sleep disturbances, and 23% from anxiety or depression [20].

In October 2020, the US National Institute for Health Research started a dynamic review on persistent COVID-19 symptoms and pointed out that not only hospitalised patients, but also those with milder courses can be affected [1]. This is confirmed by a recent longitudinal, prospective analysis of health consequences in non-hospitalised patients with mild COVID-19 symptoms. The authors observed long-lasting symptoms

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in at least 12.8% (probably up to 27.8%) of the patients with fatigue, anosmia, ageusia, and shortness of breath being most common [21]. That Long COVID symptoms are not related to the severity of COVID-19 is confirmed by a study monitoring COVID-19 patients with pneumonia. Although the frequency of Long COVID symptoms was higher in the hospitalised group (86%) compared to the outpatients (12.8%-27.8%), a correlation between COVID-19 severity during hospitalisation and symptom burden at follow-up (median of 3.8 months) could not be documented [22]. The most common symptoms of hospitalised patients were breathlessness (60%), myalgia (51.5%), anxiety (47.8%), extreme fatigue (39.6%), low mood (37.3%), and sleep disturbance (35.1%).The authors describe three symptom clusters: myalgia, fatigue; low mood, anxiety, sleep disturbance; memory impairment, attention deficit, cognitive impairment [22].

Until the end of 2020, post-viral fatigue, which is known for many viral (including SARS coronavirus) and also for bacterial and parasitic infectious diseases, was listed under the WHO indication code G93.3: Chronic Fatigue Syndrome (CFS). In January 2021, the WHO defined 2 new ICD-10 code numbers as part of the attention to COVID-19: U08.9 Personal history of COVID-19, unspecified; U09.9 for post-COVID-19 condition [23].

INTRAVENOUS VITAMIN C REDUCES FATIGUE AND CONCOMITANT SYMPTOMS IN VARIOUS DISEASES

Our recent systematic review on the effectiveness of high-dose IV vitamin C to treat fatigue identified nine clinical studies with 720 participants suffering from fatigue [24]. Three studies were randomised and controlled, one was a retrospective controlled cohort study, one a phase I study, and the remaining ones were prospective observational/before-and-after studies [24]. Three of the four controlled trials observed a significant decrease in fatigue in the vitamin C group compared to the control group ($p<0.005$). In the observational/before-and-after studies, a reduction in fatigue was reported in all studies. In the four studies that performed a statistical comparison of the pre-post levels of fatigue, a significant reduction was observed. Attendant symptoms of fatigue such as sleep disturbances, cognitive dysfunction, depression, and pain were also frequently alleviated in patients receiving IV vitamin C. Despite the different underlying diseases (cancer, surgery, infection, and allergies), vitamin C showed a significant reduction of fatigue in almost all studies except on acute post-operative fatigue. The most recent study in patients with advanced non-small cell lung cancer is particularly compelling. While fatigue continued to increase in the control group despite the best supportive therapy, it decreased significantly in the group with IV vitamin C plus hyperthermia.

A common characteristic of all these diseases is oxidative stress, which seems to be a convincing contributor to fatigue and thereby a promising biomarker of treatment [25-29]. Presumably not only acute COVID-19, but also the recovery phase of patients with Long COVID syndrome is associated with oxidative stress and a lack of antioxidants.

The vitamin C doses and the duration of treatment differ considerably in the studies on fatigue. Three of the five oncological studies used extremely high doses of vitamin C (>50 g) [30-34]. Very high doses of vitamin C show a chemotherapeutic potential that is to be fully exploited here but seem not to be necessary for improving quality of life such as by reducing fatigue [33,34]. In a review of vitamin C in cancer-associated fatigue, Carr et al. discuss the underlying mechanisms of action and conclude that the rapid correction of deficiency states, the effect as a co-factor of enzymatic reactions, and the anti-oxidative and anti-inflammatory effects are particularly important [35]. All these effects do not require extremely high doses of vitamin C. In patients with Herpes zoster, a lower dose applied in a high frequency (7.5 g every second or third day) was used. Fatigue improved in 78.2% and cognitive dysfunction in 81.8% of the patients [36]. The same dose was used for the treatment of allergies where fatigue is also a problem affecting the quality of life [37].

While in most studies the change in fatigue was evaluated after 3 or more weeks, a study in apparently healthy full-time workers displayed an acute reduction in fatigue with IV vitamin C [38]. One of the oncological studies [33] documented significant relief after one week of treatment.

STRESS AND TRAUMA IN THE PATHOGENESIS OF LONG COVID

Although the studies are still rather heterogeneous, it is already obvious that post-viral fatigue accompanied by sleep disturbances and cognitive dysfunction is also one of the most common complaints in Long COVID. This symptom cluster strongly reminds of CFS. Similar to CFS, long COVID also affects more women [22]. Besides intense fatigue, most patients with CFS report concomitant symptoms such as pain, cognitive dysfunction, and unrefreshing sleep [23,39]. CFS often begins with an infection during a period of increased physical activity or mental/somatic stress. This corresponds to the current situation in which patients with Long COVID are/were affected not only by the infection itself but probably also by mental and/or somatic stress during the lock-down. Mental and physical stress induces oxidative stress and vice versa. In CFS, including idiopathic CFS, oxidative stress, impaired sleep homeostasis, mitochondrial dysfunction, immune activation, and (neuro-) inflammation are shown to aggravate each other in a vicious pathophysiological circle [26,27].

Due to the occurrence of both physical and mental symptoms in Long COVID, some authors see parallels in the pattern of post-traumatic stress disorder (PTSD) [22]. Inflammation (especially increased IL-6) and corresponding oxidative stress is linked to various psychiatric conditions including PTSD and is associated with neuronal damage in many brain regions including the hippocampus, the amygdala, and the frontal cortex, being responsible for the regulation of stress, emotion, fear, and memory processing [40,41]. In a recent study in rats, vitamin C supplementation prevented the post-traumatic stress-induced increase in oxidative stress in the hippocampus and attenuated memory impairment [41]. Moreover, a recent review points out the putative potential of vitamin C in the treatment of stress-related disorders such as depression and anxiety. Its modulation of monoaminergic and glutamatergic neurotransmitter systems is postulated to be a pivotal cause for the antidepressant and anxiolytic effects [42].

ACUTE MICROVASCULAR DAMAGE MAY TRIGGER NEUROINFLAMMATION IN LONG COVID

A recent hypothesis is that microvascular damage in the acute phase of infection by SARS CoV-2 may trigger chronic inflammatory processes and thereby may be responsible for symptoms of Long COVID. By destroying endothelial cells, SARS CoV-2 may lead to inflammation,

thrombi (micro strokes), and consecutive brain damage [43].Neuro-inflammation contributes to the pathogenesis of neuropsychiatric symptoms due to a reduction of neurotransmitters (serotonin, dopamine, and norepinephrine) and neurotrophins, and to an increase of glutamate-induced excitotoxicity. Therefore, symptoms such as attention and cognitive deficits, new onset anxiety, depression, and fatigue consequently differ depending on the brain region involved [43,44]. In this context, it is important to consider that oxidative stress does not only reduce the bioavailability of neurotransmitters due to increased degradation, decreased formation and distribution, but it also results in a decreased concentration of vitamin C. However, vitamin C together with the vitamins B6, B12, and folic acid are important enzymatic cofactors of the synthesis of serotonin, dopamine, and noradrenaline.

Oxidative stress also plays a role in glutamate excitotoxicity: In an in vitro model of human dopaminergic neurons, vitamin C acted as a neuroprotective antioxidant being able to prevent cell death from prolonged exposure to glutamate [45].

These findings would imply starting therapy with IV vitamin C as early as possible in order to prevent vascular damage caused by SARS CoV-2 [2]. An increasing number of preclinical and clinical studies in trauma, ischemia/reperfusion, and sepsis show that oxidative stress is also a major influential factor for endothelial dysfunction and circulatory disorders, and also that high-dose IV vitamin C can combat overwhelming oxidative stress, thereby restoring endothelial and organ function [46]. In case of COVID-19, oxidative stress also triggers immune thrombosis via the formation of Neutrophil Extracellular Traps (NETs). SARS CoV-2 penetrates endothelial cells via ACE receptors and thereafter triggers a chain reaction of endothelial damage, infiltration of neutrophils, and formation of NETs [47]. Vitamin C is necessary for the phagocytosis of consumed neutrophils by macrophages. If this clearance is absent, the occurring necrosis of the neutrophils leads to NETs and thus to circulatory disorders [3,18].

DYSFUNCTIONAL IMMUNE RESPONSE IN THE PATHOGENESIS OF LONG COVID

In the study that monitored outpatients with COVID-19, a lower baseline level of SARS-CoV-2 IgG and diarrhoea during the acute infection were associated with a higher risk of developing long-term symptoms [21]. The intestine is the largest lymphatic organ and therefore very important in infection defence: An inadequate intestinal defence may play a role in persistent symptoms.

A further cause of persistent symptoms could be the induction of immune responses to self-epitopes during acute, severe COVID-19. First observations point to IgG autoantibodies widely associated with myopathies, vasculitis, and anti-phospholipid syndrome (APS) in subjects infected by SARS-CoV-2 [48,49]. The observation of autoantibodies is interesting as fatigue is a known major problem in autoimmune diseases such as multiple sclerosis, rheumatoid arthritis, diabetes mellitus type 1, systemic lupus erythematosus and inflammatory bowel diseases [27, 29, 48-52].

A recent review focuses on the similarities of thrombosis between COVID-19 and the autoimmune disease APS [53]. Molecular mimicry and endothelial dysfunction could plausibly explain the mechanism of thrombogenesis in acquired APS. Oxidative stress is etiologically involved in both processes, and the authors discuss the need for antioxidants such as vitamin C, among others. Interestingly, SARS CoV-2 downregulates the antioxidant pathway by inhibiting ACE2, NO, and endothelial NO synthase pathways resulting in generation of thrombi and activation of the coagulation cascade. Phospholipid-like epitopes that induce the formation of autoantibodies might be the S1 and S2 subunits of S protein of SARS CoV-2 or b2-glycoprotein I in host cells. Especially the latter one is changed owing to oxidative stress caused by SARS-CoV-2, creating a neo-epitope for the antibody generation. Oxidative stress plays a pathophysiological role in APS by inducing conformational changes in the b2-glycoprotein I making it more immunogenic. However, anti-phospholipids are per se not thrombogenic: Thrombogenesis needs additional factors such as endothelial injuries caused e.g. by SARS CoV-2 resulting in further oxidative stress. Vitamin C can not only restore endothelial function but also improves bioavailability of NO [46]. It is worth considering that supportive therapy with vitamin C could protect against both oxidative protein damage with subsequent immunogenicity and endothelial dysfunction.

CONCLUSION

COVID-19 is a multisystem disease in which oxidative stress is partly responsible for excessive inflammation, circulatory disorders with subsequent neuro-inflammation, and formation of autoantibodies. Of particular note are the interaction and mutual dependency of endothelial dysfunction, neuro-inflammation, and the formation of autoantibodies, all of which are triggered by oxidative stress. Oxidative stress and inflammation can cause and maintain fatigue, cognitive impairment, depression, and sleep disturbances. Various symptoms of Long COVID show parallels to those of CFS, which often begins with an infection during a period of increased stress.

Vitamin C is one of the most effective physiological antioxidants, showing anti-inflammatory effects, especially if applied IV in pharmacological doses. It restores endothelial function and is an enzymatic cofactor in the synthesis of multiple neurotransmitters. Because of its pleiotropic functions, a deficiency can aggravate the severity of illness and hamper recovery. Vitamin C deficiency has been demonstrated in COVID-19 and other severe infections; it should also be investigated in Long COVID. High-dose IV vitamin C has been investigated in patients with cancer, allergies, and herpes zoster infection. The results show a promising reduction of fatigue and common accompanying complications such as sleep disturbances, depressive symptoms, pain, and cognitive disorders. Due to various underlying pathophysiological similarities, this also might work in Long COVID.

COMPETING INTERESTS

KK declares that she has no competing interests. CV is employed part time at Pascoe Pharmazeutische Praeparate GmbH (Giessen, Germany).

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