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EDITORIAL

The antiviral properties of vitamin C

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1. Introduction

There is a growing interest in the administration of vitamin C beyond the treatment of hypovitaminosis C in malnourished patients. This has been driven by a 2016 'before-after' study which suggested a substantial survival benefit from a protocol that included hydrocortisone, ascorbic acid (vitamin C) and thiamine (HAT therapy) in the treatment of patients with severe sepsis and septic shock [1]. Currently, Clinical trials.gov lists 29 ongoing or completed trials investigating vitamin C administration in sepsis. Historically, there has been misguided and erroneous suggestions of the effectiveness of vitamin C in promoting longevity, preventing and treating the common cold [2], and a collection of poorly evidenced health claims, encouraged by a multi-billion dollar over the counter vitamin supplement industry. Many of the misconceptions regarding vitamin C were perpetuated by two-times Nobel Laureate Linus Pauling [3,4]. The revival of interest in vitamin C therapy for acute inflammatory disorders, grounded in sound biological rationale, follows decades of research. The current focus of interest centers on bacterial sepsis and septic shock in critically ill patients. Over 300 basic science and clinical studies provide strong mechanistic data to support the use of vitamin C in this setting [5,6]. There is, however, emerging literature to suggest that vitamin C may play an adjunctive role in the treatment of a variety of viral infections. The purpose of this article is to review the biological rationale and evidence for the administration of vitamin C in viral infections.

2. Biologic rationale of vitamin C in viral infections

A number of observers including Linus Pauling have suggested that vitamin C in high dosages is directly virucidal [3]. This assumption was based on *in-vitro* studies, where very high doses of vitamin C, in the presence of free copper and/or iron, has virucidal activity, presumably through the generation of hydrogen peroxide and other radical species [7,8]. In addition, a low pH may have contributed to the *in-vitro* antiviral effects of vitamin C.; However, it is most unlikely that vitamin C is directly virucidal *in-vivo*. It is now well recognized that while vitamin C is a potent antioxidant, at high pharmacologic concentrations it can paradoxically exert pro-oxidant effects (generation of reactive oxygen species) via the reduction of transition metal [9]. Avici et al demonstrated that very high-dose sodium ascorbate (90mM) kills *Candida albicans in-vitro* via the iron-catalyzed Fenton reaction [10]. However, this effect was completely inhibited by the iron chelator 2,2'-bipyridyl. Nevertheless, an experimental model demonstrated that vitamin C decreased the viral load of Ebstein-Barr virus (EBV) infected cells [11]. This suggests that other mechanism must be at play. Cinatl and coworkers demonstrated that pretreatment of human foreskin fibroblast and endothelial cells with vitamin C prior to cytomegalovirus (CMV) infection significantly reduced the expression of viral antigens and the cellular viral load [12]. This finding was not reproduced when the vitamin C was added after the virus infection. The authors concluded that this effect was likely due to the immunomodulatory properties of vitamin C, rather than a direct antiviral effect. Vitamin C is concentrated in leucocytes, lymphocytes, and macrophages reaching high concentrations in these cells [13,14]. Vitamin C improves chemotaxis, enhances neutrophil phagocytic capacity and oxidative killing and supports lymphocyte proliferation and function [13,15,16].

L-gulono-γ-lactone oxidase (Gulo) is the rate-limiting last step of vitamin C biosynthesis in animals. However, anthropoid primates and guinea pigs have lost the ability to synthesize vitamin C due to mutations in the gene of this enzyme. Gulo (-/-) knockout mice provide a model to study the role of vitamin C insufficiency in viral infections; a 'humanized-mouse' model of infection. Kim et al demonstrated that nasal inoculation of H3N2 influenza virus was highly lethal in Gulo (-/-) mice as compared to wild type mice [17]. In this study, viral titers in the lung of vitamin C-insufficient *Gulo (-/-)* mice were increased, while production of the anti-viral cytokine interferon (IFN)-α/β was decreased. Furthermore, the infiltration of inflammatory cells into the lung and production of pro-inflammatory cytokines, tumor necrosis factor (TNF) and interleukin-1 (IL-1)-α/β was increased in the lung. These effects were corrected in Gulo (-/-) mice repleted with vitamin C prior to viral exposure. Impaired phosphorylation of signal transducers and activators of transcription (STATs) may underlie the deceased production of IFN in Gulo (-/-) mice [17]. Similarly, Li et al demonstrated that Gulo (-/-) mice as compared to wild type mice had an impaired immune

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response with greater lung pathological injury when exposed to influenza H1N1 virus [18]. Cai et al demonstrated that restraint-stressed mice (mice that are physically restrained in a restraint tube) with H1N1 induced pneumonia, demonstrated a dose-dependent reduction of mortality with vitamin C and histopathological lung sections showed reduced injury in the treated mice [19]. In this study, administration of vitamin C significantly recovered the diminished mitochondrial membrane potential and deceased the gene expression of pro-inflammatory cytokines. In addition to demonstrating activity against influenza and herpes virus, vitamin C has been reported to have activity against a number of other viruses including poliovirus, Venezuelan equine encephalitis, human lymphotropic virus type 1 (HTLV-1), human immunodeficiency virus (HIV), parvovirus and rabies virus among others [20–27].

Many infections lead to the activation of phagocytes, with the release of reactive oxygen species (ROS). ROS play a role in the deactivation of viruses. However, many of the ROS are harmful to the host cells and may be involved in the pathogenesis of viral induced host injury. Respiratory syncytial virus (RSV) is one of the most important causes of upper and lower respiratory tract infections in infants and young children. RSV infection of airway epithelial cells induces ROS production with inhibition of lung antioxidant enzymes; this oxidant-antioxidant cellular imbalance plays a major role in RSV pulmonary toxicity [28]. In an experimental model, antioxidant administration significantly reduced lung pulmonary inflammation and lung injury [29]. Vitamin C is a potent antioxidant, which directly scavenges oxygen free radicals as well as restoring other cellular antioxidants including tetrahydrobiopterin and α-tocopherol [5,14]. Vitamin C may, therefore, ameliorate viral-induced oxidative injury.

3. Clinical evidence of efficacy in viral infections

The suggestion that vitamin C may be beneficial in a number of viral infections is based on two concepts, namely, i) patients with acute infectious diseases have low circulating vitamin C levels (likely due to metabolic consumption) [9,30], and ii) vitamin C has beneficial immunomodulating properties in patients with viral infections, predominantly by increasing the production of α/β interferons and downregulating the production of pro-inflammatory cytokines (as discussed above). Despite the biological plausibility that vitamin C may be beneficial in viral infections, there is limited evidence-based clinical data to support this contention. Largely driven by the controversy generated by Linus Pauling's popularization of vitamin C for the treatment of the 'common cold,' most of the randomized controlled trials (RCTs') conducted to date have focused on the role of vitamin C in the prevention and treatment of this syndrome. In a meta-analysis of 29 RCTS, Hemila and Chalker demonstrated the failure of vitamin C supplementation to reduce the incidence of colds in the general population [2]. Furthermore, no consistent effect of vitamin C was seen on the duration or severity of colds. Methodological issues with many of the studies included in this meta-analysis (most published prior to 1980), the variable vitamin C dosage in the treatment group and failure to control vitamin C intake in the control groups complicate the interpretation of these studies.

Vitamin C appears to have clinical benefits in patients with infections due to a number of herpes viruses. Herpes zoster (HZV) infection results from the reactivation of latent Varicella-Zoster virus (VZV) generally due to an age-related loss of cell-mediated immunity. Chen et al demonstrated that plasma concentrations of vitamin C are reduced in post-herpetic neuralgia patients when compared to healthy volunteers (4.6 ± 3.1 vs 13.5 ± 6.0 mg/L; $p < 0.001$) [31]. These authors then performed a double-blinded, RCT in which 41 patients were randomly allocated to receive intravenous vitamin C (50mg/kg on days 1, 3 and 5) or placebo [31]. Those patients who received vitamin C had a significant reduction in their pain scale scores by day 7. In a non-blinded RCT, the effect of vitamin C on acute herpetic pain and postherpetic neuralgia was evaluated [32]. In this study, 87 patients were randomized to receive 5g of intravenous vitamin C on the first, third and fifth days or placebo. While there was no difference between groups in the severity and duration of pain during the acute phase, the treatment group exhibited a lower incidence of postherpetic neuralgia (31.1% vs. 57.1%, $p < 0.05$) and a lower pain score at 8 weeks (0.64 ± 0.9 vs. 1.98 ± 0.7, $p = 004$) [32]. Vitamin C is concentrated in the aqueous humor of the anterior chamber of the eye. A retrospective cohort study indicated that oral vitamin C reduced the risk of herpes simplex keratitis recurrence particularly in combination with oral antiviral therapy [33].

4. The urgent need for additional research

Influenza A virus is responsible for regular epidemics and pandemics that claim thousands of lives annually. While experimental models demonstrate a beneficial effect of vitamin C in influenza infections (as reviewed above), this therapy has not been reported in patients. Anecdotally, we have treated about a dozen patients with life-threatening respiratory failure due to influenza A infection with our modified HAT protocol (without corticosteroids); these patients demonstrated a rapid improvement after initiation of this therapy. It should be emphasized that the role of corticosteroids in patients with viral infections is complex; corticosteroids may modulate the inflammatory response, however, on the other hand, they may stimulate the infection. Currently, corticosteroids are not recommended in patients with severe influenza A infections [34,35]. Well-designed clinical trials are urgently required to study the use of vitamin C as adjunctive therapy in serious infections due to influenza, RSV, herpes, and other common viral illnesses.

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