

High Dose Of Ascorbic Acid Used In Sars Covid-19 Treatment: Scientific And Clinical Support For Its Therapeutic Implementation

Utilización de altas dosis de ácido ascórbico en el tratamiento del SARS Covid-19: Soporte Científico y Clínico para su aplicación en terapéutica

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RESUMEN

El coronavirus 2019 (SARS-CoV-2) ha sido declarado una emergencia de salud pública de impacto internacional por la Organización Mundial de la Salud. Debido a la aparición repentina de este proceso pandémico asociado con alta morbilidad y la mortalidad en todo el mundo, se han implementado varios tratamientos en los pacientes aquejados con esta dolencia. En este marco, comenzaron a usarse en pacientes críticos altas dosis de vitamina C.

En este trabajo, analizamos los ensayos clínicos y / o trabajos de investigación disponibles en la literatura. Aunque se necesita más evidencia sobre su efectividad, es importante que el especialista comprenda la lógica clínica de este uso para determinar si es correcto como tratamiento concomitante.

Conclusiones: El uso de altas dosis de vitamina C por vía parenteral parece ser una alternativa segura, disponible y económica, especialmente para pacientes críticos.

Palabras clave: Covid-19; Tratamiento; Vitamina C

ABSTRACT

The 2019 coronavirus (SARS-CoV-2) has been declared a public health emergency of international concern by the World Health Organization. Due to the sudden appearance of this pandemic process associated with increasing morbidity and mortality worldwide, various treatments have been implemented. In this framework, high doses of vitamin C began to be used in critically ill patients.

We analyze the clinical trials and/or research papers available in the literature. Although more evidence on its effectiveness is needed is important for the specialist to understand the clinical logic of this use to determine if it is correct as a concomitant treatment.

Conclusions: It seems that using high doses of vitamin C parenterally is a safe, available and economical alternative especially for critically ill patients.

Keywords: Covid-19; Treatment; Vitamin C

INTRODUCTION

SARS (Severe Acute Respiratory Syndrome) coronavirus (SARS-CoV) is a virus identified in 2003. SARS-CoV is thought to be an animal virus from an as-yet-uncertain animal reservoir, perhaps bats, that spread to other animals (civet cats) and first infected humans in the Guangdong province of southern China in 2002⁽¹⁾. The 2019 novel coronavirus (SARS-CoV-2) epidemic, which was first reported in December 2019 in Wuhan, China, and has been declared a public health emergency of international concern by the World Health Organization, may progress to a pandemic associated with substantial morbidity and mortality⁽²⁾. This novel coronavirus was officially named as Corona Virus Disease 2019 (COVID-19) by WHO. Due to the sudden appearance of this pandemic process, various treatments have been im-

plemented using antivirals, antibiotics, antimalarials, corticosteroids, etc.⁽³⁾. On an almost empirical basis, high doses of vitamin C began to be used in critically ill patients so it is important for specialist to understand the clinical logic of this use in order to determine if it is correct as a concomitant treatment.

Vitamin C or ascorbic acid (AA) is the main non-enzymatic, water-soluble antioxidant present in plasma⁽⁴⁾. The main functions of vitamin C are neutralizing free radicals, reducing iron, regenerating vitamin E and acting as a cofactor of α -ketoglutarate enzymes dioxygenases. These enzymes participate in the synthesis of neurotransmitters, in the regulation of gene expression and in the crosslinking of collagen fibers⁽⁵⁾.

Vitamin C works in the human body as a free radical scavenger, and for this reason, it prevents cell damage induced by free radicals⁽⁶⁾, providing protection against various disorders such as arthritis, atherosclerosis, cancer, diabetes, and ischemia, among others, that involve oxidative stress^(7,8).

As it is well known, this vitamin must be incorporated into the diet and supplemented in many cases to achieve all its beneficial effects for health⁽⁹⁾.

The absorption of vitamin C from the diet depends on a multiplicity of factors that depend on the facilitated diffusion and on a substrate transport mechanism that involves the specific transporters of ascorbates, whose saturation and low expression control the effectiveness of serum vitamin C concentration.

In this context, a large number of formulations containing ascorbic acid are available for the oral route, but when high doses are required, parenteral administrations are required. It is known that plasma vitamin C concentrations are usually below normal in critically ill patients⁽¹⁰⁾, inversely correlating with multi-organ failure⁽¹¹⁾, and directly with survival rates⁽¹²⁾, which highlights the importance of this vitamin in the treatment and progress of this type of patient⁽¹³⁾.

It is estimated that 40% of critically ill patients with septic shock have serum vitamin C levels that suggest scurvy (<11.3 $\mu\text{mol/l}$). Since vitamin C is an essential element in the generation of endogenous vasopressors and also a potential mediator in maintaining the response capacity of vascular vasopressors, an acute deficiency can contribute to hypotension, exaggerated inflammation, capillary leak and microcirculatory compromise⁽¹⁴⁾.

Vitamin C may also function as a weak antihistamine agent to provide relief from flu-like symptoms such as sneezing,

a running or stuffy nose, and swollen sinuses. Three human controlled trials have reported that there was significantly lower incidence of pneumonia in vitamin C-supplemented groups, suggesting that vitamin C might reduce the susceptibility to lower respiratory tract infections under certain conditions. COVID-19 has been reported to cause lower respiratory tract infection, so vitamin C could be one of the effective choices for the treatment of COVID-19⁽¹⁵⁾.

MATERIAL AND METHODS

To understand these assumptions in detail, we analyze the clinical trials and/or research papers available in the literature.

The search strategy was based on the combination of terms Mesh (Medical Subject Headings) and keywords related to each term, combined by the boolean operators AND, OR and NOT.

The keywords of interest used to identify terms were "Virus Diseases"; "Respiratory Insufficiency"; "Viremia"; "Pneumonia"; "coronavirus"; "COVID"; "Sepsis"; "Ascorbic Acid"; "Vitamins [Pharmacological Action]". Also, the additional requirement that the articles correspond to clinical studies, or reviews thereof, was taken into account. Therefore, terms and keywords related to them were introduced.

The databases consulted for the identification of the studies were: Pubmed (www.ncbi.nlm.nih.gov) and SCOPUS (www.scopus.com). The strategies were complemented by searches of the registry for clinical trials (clinicaltrials.gov).

RESULTS AND DISCUSSION

Regarding the adverse effects that this therapy can potentially bring, there are antecedents of several studies in which patients with respiratory pathologies were randomized to receive intravenous infusion of vitamin C (50 mg/kg in 5% dextrose in water, n=84/day), there were no study-related unexpected adverse events during the trial⁽¹⁶⁾.

In a phase I safety trial of intravenous ascorbic acid in patients with severe sepsis, no patient on low- or high-dose of ascorbic acid treated suffered any identifiable adverse events⁽¹⁷⁾. Dosing protocols for this trial emerged from the preclinical research. Subjects were assigned to any of three dosing groups (0 mg/kg/day, 50 mg/kg/day, or 200 mg/kg/day) in a 1:1:1 ratio using a randomized scheme generated by using Research Randomizer⁽¹⁸⁾. Nathens et al. administered 1 gram of ascorbic acid every 8 hours for 28 days to critically ill patients without adverse effects⁽¹⁹⁾. Tanaka et al. administered 66 mg/kg/hour for 24 hours to patients with burns on 50% of the surface area without adverse events⁽²⁰⁾. Hoffer et al. administered up to 90 grams of

ascorbic acid intravenously 3 times a week to patients with advanced malignancy without adverse events⁽²¹⁾.

However, renal failure following treatment with ascorbic acid has been reported in another study in patients with pre-existing renal disorders⁽²²⁾. A phase I clinical trial evaluated the safety of combining high-dose intravenous ascorbate with gemcitabine in patients with stage IV pancreatic cancer. The patients tolerated the combination therapy well and no significant adverse effects were reported⁽²³⁾.

In general, high intravenous doses of ascorbic acid, even associated with malignant tumors, were well tolerated in clinical trials^(24,25).

In terms of effectiveness, vitamin C has been studied in a variety of dosage regimens (25-200 mg/kg/day IV) for different critical clinical conditions including sepsis, burns, trauma and acute respiratory distress syndrome (ARDS)⁽²⁶⁾.

Evidence suggests that vitamin C administration may reduce the need for vasopressor support⁽²⁷⁾, shorten the duration of mechanical ventilation⁽²⁸⁾, and the length of stay in the ICU⁽²⁹⁾.

Regarding the treatment of sepsis, until 2019, the quality and quantity of evidence was still insufficient to draw firm conclusions⁽³⁰⁾. In October of last year, the largest completed trial on vitamin C as a treatment for sepsis was published⁽¹⁶⁾. The CITRIS-ALI trial was a double-blind, controlled, multicenter trial, enrolling 167 patients with sepsis and ARDS who were randomized to receive 50 mg/kg every 6 h of high dose intravenous vitamin C (HDIVC) for 4 days versus placebo.

Although it was a secondary result, the study showed a statistically significant difference in all-cause mortality at 28 days (29.8% in the HDIVC group vs 46.3% in the placebo group, p value <0.05). The Kaplan-Meier survival curves for the 2 groups were significantly different using the Wilcoxon test ($\chi^2 = 6.5$; $p = 0.01$). Furthermore, the group treated with vitamin C showed more ICU-free days at day 28 (10.7, HDIVC vs. 7.7, placebo, $p = 0.03$), more days without hospitalization (22.6 HDIVC vs. 15.5 placebo, $p = 0.04$) and more days without ventilator (13.1 HDIVC vs. 10.6 placebo, $p = 0.15$). In view of this results and because of the emergency of SARS-CoV-2, the Arnas Civico-di Cristina-Benfratelli National Relevance Hospital in Palermo, has decided to treat patients with 10 grams of vitamin C in 250 ml of saline to infuse at a rate of 60 drops/minute⁽³¹⁾. The clinical evolution of the included patients (who signed an informed consent) will be recorded as part of a longitudinal study.

Considering that the high doses of vitamin C are of negligible cost and that they have not shown any significant side effect, any decrease in days of hospitalization, ICU and mortality, makes its exploration worthwhile.

In a pandemic context such as the current one, it is important to use the evidence to achieve appropriate and useful therapies. Recently, the information on the use of different medications for the treatment of COVID-19 has been increasing quickly.

CONCLUSION

Although more evidence on its effectiveness is needed, it seems that using high doses of vitamin C parenterally is a safe, available and economical alternative especially for critically ill patients.

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