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Parenteral Ascorbic Acid for Treatment of Sepsis

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Abstract

Sepsis kills nearly 1 million people each year in the United States and sepsis-related hospitalizations cost approximately $24 billion annually (Paoli, Reynolds, Sinha, Gitlin, & Crouser, 2018). Current treatment guidelines are limited to targeted antibiotics and hemodynamic support. While antibiotics are the definitive treatment to eradicate the infectious pathogen, there are currently no standard-of-care treatments that consistently and successfully attenuate the damage sustained to the body by its own inflammatory response to infection. Many different treatments have been trialed and failed to show improved outcomes. Vitamin C, or ascorbic acid, has long been associated with supporting immune function, and has been studied in the past in various related capacities. More recently, a study initiated by Dr. Paul Marik has spurred much discussion and additional research regarding the potential use of ascorbic acid as an adjunctive treatment for sepsis patients. Research suggests that it may reduce damage by reducing oxidative stress, regulate the body's immune response, and facilitating the production of endogenous vasopressin. Discussion will include the mechanism of action of ascorbic acid in the body, its potential role, efficacy, and safety in the treatment of sepsis, as well as additional treatment components. Also discussed is the cost in both dollars and mortality, of waiting to implement the widespread use of what appears in some studies to be a low-cost, low-risk, high-reward treatment.

Introduction

Sepsis is an ongoing cause of morbidity and mortality in the United States. It is the most common discharge diagnosis for adult patients and the costliest major cause of inpatient admissions (Esposito et al., 2018). The standard of care treatment involves early identification of infection, fluid resuscitation, and broad-spectrum intravenous (IV) antibiotics until cultures can assist with narrowing to a specific pathogen (Rhodes et al., 2017). Unfortunately, in the time that it can take to identify the source of infection, many patients progress to septic shock, which carries a mortality rate of up to 80% (Paoli et al., 2018). Sepsis is loosely defined as a systemic infection that causes organ dysfunction due to the body's immune response. Part of the dysregulation of the immune response involves inflammation, oxidative stress, and the body's subsequent response. Given its antioxidant properties, the theoretical use of vitamin C supplementation in sepsis is not necessarily new, but is being studied more intensely in recent years, largely due to a promising 2016 retrospective study by Dr. Paul E. Marik of Norfolk, Virginia.

Statement of the Problem

In the United States, nearly 1 million patients are admitted each year for sepsis. Many sources suggest that the incidence is increasing. One study reports an increase of 8.7% per year over the course of 20-years. More than half of all inpatient deaths are due to infection. In addition to the lives lost, sepsis draws a large amount of money and resources.

The average inpatient length of stay for a patient with sepsis is 75% longer than for other illnesses, requiring corresponding supplies and staffing. In 2013, only 3.6% of hospital stays were due to sepsis, but this population utilized 13% of the cost of resources at approximately $24 billion. (Paoli, et al., 2018) Oxidative stress on vasculature during acute sepsis can lead to hemodynamic instability, increased inflammation, and death. Patients who progress from sepsis to septic shock have mortality rates of approximately 30-50% (Carr, Shaw, Fowler, & Natarajan, 2015). Aside from current antibiotics, there are no other mainstay medications in treatment of sepsis.

Research Questions

- What is the role of ascorbic acid in the human body and what theoretical mechanisms of action does it have in a patient with sepsis?
- In patients with sepsis, has administration of intravenous ascorbic acid been shown to decrease mortality rates when compared to current standard of care?
- At what dose might there be increased benefit from ascorbic acid supplementation, and is that dose beyond the standard replacement from enteral or parenteral nutrition that is routinely administered to critically ill patients?
- In treatment of sepsis, is intravenous ascorbic acid a cost effective treatment when combined with the current regimen of intravenous fluid resuscitation and antibiotic therapy? What are the risks and benefits to delaying implementation of this treatment option?

Literature Review

Mechanism of action

Vitamin C (ascorbic acid) has been proven to play many major roles in the normal function of the human body. The antioxidant properties of ascorbic acid help to prevent oxidative stress from causing damage to cellular proteins. It also aids in the creation and function of similarly-acting components. It helps to produce catecholamines, cortisol, and vasopressin (Moscowitz et al., 2018). It is a vital part of growth and repair of tissues due to its role in collagen formation, which is utilized throughout the body in many areas, including tendons, ligaments, and vasculature.

Safety and Efficacy

In a randomized, double-blind, placebo-controlled trial by Fowler et al., 2014, no patients were removed from the study due to adverse events after receiving low or high-dose IV ascorbic acid. Marik (2017) has been credited with bringing this treatment into the public eye most recently. His study evaluated outcomes of 94 patients being treated for sepsis. The primary outcome evaluated was in-hospital survival. He used a combination of ascorbic acid, thiamine, and hydrocortisone to treat 47 patients and then retrospectively matched them to previous patients with similar conditions who had been treated using only traditional standard of care for sepsis. The results appear to be dramatic.

The treatment group saw only 4 fatalities, and no patients developed progressive organ failure. Carr et al., (2017) found that C-reactive protein levels were shown to be inversely related to that of serum vitamin C levels, and supplementation of vitamin C appeared to cause C-reactive protein levels to decrease.

Benefits at low vs high doses

In Fowler et al, 2014, the patients who received the high-dose ascorbic acid (200mg/kg) saw a faster rate of improvement in terms of decreasing need for exogenous vasopressors and decreased need for mechanical ventilation when compared to patients who were given low-dose ascorbic acid (50mg/kg) or placebo.

Cost of delaying new treatments

Due to the fact that the treatment components themselves are relatively low cost, and the fact that thiamine and hydrocortisone, as well as ascorbic acid in smaller doses, are already often administered to critically-ill patients, and the lack of evidence demonstrating serious adverse effects from high-dose ascorbic acid, it seems reasonable in this case to consider early implementation of this adjunct sepsis treatment. The major flaw in this discussion is that since this treatment is not being widely used, the costs and patient outcomes were theoretical and based on an observational study with a small sample size. More specific cost estimates for the treatment as well as for training of staff could be useful to aid in decision-making (Blythe, Cook, & Graves, 2018).

Discussion

Due to the large incidence and society cost of sepsis and its sequelae, this has long been a major area of research. Several novel sepsis treatments have appeared promising and failed to produce meaningful results at the clinical trial level. Although the seemingly-dramatic outcomes have been met with skepticism by many, the current literature suggests that ascorbic acid may be the most promising new treatment for sepsis that clinicians have seen in a very long time. Its mechanism of action in the body serves many roles that are not only vital to the healthy individual, but physiologically suffering in cases of sepsis. As previously mentioned, there are several currently active clinical trials studying the use of intravenous ascorbic acid in treating patients with sepsis. Within the next few years, antioxidant therapy may become a viable treatment adjunct for patients with severe sepsis. At a minimum, if it shows enough benefit in early trials, the relatively low cost as well as lack of risk of adverse effects may allow it to be implemented as part of a sepsis protocol. In addition to larger sample sizes and blind, placebo-controlled trials, a specific dosing recommendation would need to be established, as well as at what point ascorbic acid would be administered during the timeline of the sepsis protocol.

Applicability to Clinical Practice

As stated, there are several trials currently in various stages. There are several areas that will need to be addressed before widespread implementation can take place. While this research currently applies to critical care as opposed to primary care, significant benefit from use of high-dose ascorbic acid in infectious disease could translate to research its use in less severe illness. As more research becomes available, the use of parenteral ascorbic acid could be a life-saving and cost-effective treatment option for patients with severe sepsis.

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