The Physiological Basis for Vitamin C as a Potential Treatment for Sepsis

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Abstract: Accounting for one third of all hospital patient deaths in America, sepsis remains one of the most deadly and complicated conditions that healthcare providers treat. Septic shock, a progressed form of sepsis, is even more troublesome, as mortality rates typically fall between 50-72%. It has been proposed that administration of high doses of vitamin C could be an effective treatment for the condition due to the nutrient’s anti-stress and anti-shock properties. This investigation of the physiological reasoning for administering high doses of vitamin C evaluates the viability of its use in patients with septic shock.

It’s a grim diagnosis that no patient or family member is prepared to hear, yet one that threatens the lives of hospitals’ sickest patients. Septic shock is an unforgiving condition with a poor prognosis unless caught and treated early. By definition, sepsis is the systemic release of inflammatory mediators in response to a serious infection in the blood. Though this is typically treatable, if left uncontrolled it can progress to septic shock and cause dangerous hypotension. It might be perplexing that the body’s natural response to an infection is the root cause of such a grave disease, but its systemic nature of inflammation causes life-threatening complications. Afflicting 1.7 million Americans each year, sepsis alone is responsible for one third of all patient deaths that occur in a hospital. Of the septic patients who progress into shock, mortality rates are typically between 50-72% depending on the infection’s origin. Because of the nutrient’s vital role in coordinating the body’s stress and shock responses, physicians are beginning to look towards vitamin C as a novel method of treating critically ill septic shock patients.

When an infection is present, a typical immune response involves a cascade of events that prepare affected tissues for an influx of white blood cells to fight off foreign substances. One event involved in this cascade is the increased permeability of tissue endothelium to allow for easier transport of immune cells from the circulation to the site of infection. Septic shock, unlike localized infection, is characterized by increased endothelial permeability throughout the body. This causes a severe drop in blood pressure as blood rushes out of the vessels, through the endothelium, and into internal organs. Such a swift displacement of blood causes a myriad of further complications including tissue hypoxia, free radical accumulation, inhibition of catecholamine release, and systemic distribution of inflammatory mediators. If not immediately addressed, septic shock will ultimately lead to organ failure and death.

Current methods of treatment involve administration of large volumes of fluids, antibiotics, and vasopressors to stimulate an increase in blood pressure, but these are only effective if the condition is caught early. Hundreds of proposed treatments have progressed to late-phase clinical trials, but none have been effective in treating the systemic concerns of inflammation and cellular stress that typically precede organ failure in septic shock patients. But why do researchers look towards vitamin C as a treatment? While many key nutrients are depleted during septic shock, the majority are merely indicators of disease. Replacing these nutrients could be hazardous to the patient and further exaggerate the inflammatory response. Upon closer examination, scientists have found that vitamin C plays a vital role in many of the body’s natural processes that are typically suppressed in those with septic shock. This is evident in the various ways that vitamin C is linked to the maintenance of stable blood pressure.

The primary cause of acute hypotension in septic shock patients is the sudden transfer of blood volume from the circulation to organ tissues due to the thinning of endothelial linings throughout the body. In a healthy individual, vitamin C is imperative in maintaining strong endothelial tissue and preventing premature apoptosis of endothelial cells. Aside from maintaining the integrity of endothelium, vitamin C also enables blood vessels to respond to vasoconstrictors. In an attempt to elevate blood pressure, these compounds tighten blood vessels by causing smooth muscle contraction. In a septic shock patient, this pathway is inhibited by the enzyme, inducible nitric oxide synthase (iNOS) which counteracts vasoconstrictors’ effects and prevents blood vessels from effectively constricting in response to low blood pressure. Studies have shown that when vitamin C is reintroduced into the environment, it is successful in blocking endothelial iNOS and in effect allows vasoconstrictors to re-establish a stabilized blood pressure.

In addition to vasoconstrictors, other compounds work together to compensate for severe hypotension. Vasopressin, also known as antidiuretic hormone (ADH), is a prime example of one of these compounds. In a healthy individual, ADH is heavily involved in the maintenance of an individual’s fluid balance and helps natural fluctuations in blood volume. When blood volume is extremely low during septic shock, ADH signals the kidneys to retain water in body circulation to compensate for fluid lost through the endothelium. While septic shock patients will likely experience significantly heightened levels of vasopressin at the onset of the condition, ADH levels diminish thereafter as vitamin C, a necessary cofactor in ADH production, is quickly depleted. As a result, their blood pressure will continue to drop unless their physicians are able to reverse it in the early stages.
Vasopressin has multiple roles in the body that are not limited to just maintaining fluid balance. It additionally allows for the release of a substance called adrenocorticotropic hormone (ACTH), which causes the release of catecholamines like dopamine and epinephrine. These compounds are able to increase the heart’s contractility and as a result, heighten the amount of blood circulating through the patient’s body. This is a desirable outcome in the case of septic shock patients. As would be expected, the inability to synthesize vasopressin due to a lack of vitamin C would result in serious dangers for a normal individual, but the consequences are even graver for septic shock patients who need dopamine and epinephrine to increase their cardiac output.

A direct result of severe hypotension, the trademark symptom of septic shock, is the concern of systemic hypoxia, or lack of oxygen throughout the body’s tissues. When tissues are in an oxygen-deprived state, they begin to produce extensive amounts of reactive oxygen species (ROS) which puts the tissues under a great deal of oxidative stress. Such stress causes damage to cells’ organelles, and if the build-up of ROS becomes severe enough, it threatens the functionality of endothelial cells. Vitamin C offers two possible solutions to this problem. It is capable of collecting ROS itself and is also capable of activating other ROS scavengers within the cell. By reducing the amount of ROS in the cell, the degree of cell damage from oxidative stress is effectively limited. Because of this, it is assumed that vitamin C could protect endothelial cells from further damage and in effect, prevent the infection from worsening.

Outside of vitamin C’s direct effects on blood pressure and oxidative stress, the nutrient also has more generic roles in the body that could be beneficial for septic shock patients. Because the underlying issue with septic shock is systemic inflammation, it should not come as a surprise to learn that inflammatory mediators are distributed throughout the body in a patient with this condition. The systemic presence of these molecules exacerbate the situation, because they encourage thinning of the endothelial layers and loosening at the junctions between endothelial cells, allowing a greater volume of blood to leave circulation. Studies have found that when ample amounts of vitamin C are present, the release of inflammatory mediators is blocked and the integrity of the endothelium is preserved. Vitamin C also supports immune function as it is found in high concentrations in white blood cells and aids in chemotaxis which summons immune cells to the site of infection.

Despite strong rationale for the multi-faceted ability of vitamin C to reverse the effects of septic shock, physicians still have concerns with this treatment. One of the most prominent troubles with the idea of vitamin C usage is the possibility that individuals could develop renal failure as a result of administering doses as high as 6 grams daily to the patients. A study conducted through the University of Kansas Medical Center addressed this concern by surveying side effects observed by hospital physicians who had prescribed high doses of intravenous vitamin C to their patients at any point over the course of the previous year. Researchers found that the most prevalent side effect in patients was fatigue, noted in 59 of 9286 patients. In the same sample of patients, only one was reported to have developed kidney failure by the end of the study and this particular patient had known renal tumors prior to the vitamin C treatment. To minimize the risk of patients falling into kidney failure after high dose vitamin C treatment, one physician found anecdotal success in administering a cocktail of hydrocortisone and thiamine (vitamin B₁) with vitamin C to his septic shock patients. The rationale is that renal failure would be a result of oxalate crystallization in the kidneys, but the presence of vitamin B₁₂ reduces conversion of glyoxylate to oxalate so the likelihood of oxalate crystallization, and therefore kidney failure, would theoretically be much lower. While the ideology of a cocktail treatment like this one is plausible, further research needs to be conducted to determine its true efficacy.

To assess the safety of administering high concentration, intravenous vitamin C to severe septic shock patients, a team of researchers led by Dr. Fowler of Virginia Commonwealth University’s School of Medicine conducted a study that collected patients’ responses to varying concentrations of vitamin C. A medical professional monitored patients’ vital signs in 5-minute intervals during and following the infusion and was instructed to remove the patient from treatment if any adverse effects were observed. At the conclusion of the study, the medical team reported zero adverse effects and improved organ function in the high dose vitamin C group. A different team of researchers conducted a similar study but focused on determining vitamin C’s role in maintaining a stable blood pressure. They found that the treatment group experienced lower mortality rates and required lower doses of exogenous vasopressors to maintain a sufficient blood pressure. Despite the encouraging findings of these studies, they share common limitations. Both had a small sample size (n=24 and n=28, respectively) and implemented inclusion criteria for the safety of the patients. While these study designs provide useful dosing information, their results cannot be generalized to fit the total septic shock population. In hopes of overcoming these limitations and reaching a reliable conclusion on the safety and efficacy of administering high doses of vitamin C to septic shock patients, two large-scale, double blind studies are currently being conducted in the United States and are expected to be completed in April 2019.

Research like this is exciting because the use of vitamin C to treat septic shock patients would be transformative considering its potential ability to act on many of the body systems affected by septic shock. From maintaining endothelial integrity and encouraging vasoconstrictor functionality, to aiding in the production of catecholamines and reducing oxidative stress within body cells, it is clear that vitamin C plays a vital role in many body processes at risk in septic shock. If high concentration, intravenous vitamin C administration is determined to be both safe and successful in treating the entire spectrum of septic shock patients, then the prognosis for the disease would be much less daunting. This treatment method would be incredibly inexpensive, especially when compared to the currently available high-cost treatments that yield questionable success rates. A treatment as simple as vitamin C would also be accessible across the world and would not be limited to areas with the most advanced and expensive medical
Only time will tell if the treatment will live up to the hype that it is inspiring, but at least for now it is providing a ray of hope to an otherwise difficult to manage condition.

References


