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Review Article

VITAMIN C IN SEPSIS: A VIABLE ADJUNCTIVE THERAPY

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ABSTRACT

Sepsis is a host immune response disorder caused by infection, which is often developed into life-threatening organ dysfunction and refractory hypotension in the latest clinical stage, and is characterized by poor prognosis and high mortality. Studies have shown that vitamin C has the effects of antioxidant, anti-inflammatory, improving immune function and organ dysfunction in patients, and can effectively improve the mortality and prognosis of patients with sepsis. As a result, vitamin C can be used as an effective adjunct treatment for sepsis. In this paper, the mechanisms of action of vitamin C in sepsis and research advances will be reviewd.

Keywords: sepsis vitamin C treatment mechanism

INTRODUCTION

Sepsis is a lethal organ dysfunction syndrome caused by systemic inflammation. In order to seek an understanding of its nature, people continue to propose a more comprehensive concept. The third international consensus on the definition of sepsis was proposed in 2016. That is, Sepsis 3.0 is the currently recognized definition of sepsis in the world. It defines sepsis as: infection causes host immune response imbalance, leading to life-threatening organ dysfunction[1].Sepsis has always been one of the most common and deadly clinical diseases. Over the past few years, the incidence of sepsis in my country has remained high. Studies have shown that the incidence of sepsis in the ICU is 20.6%, and the mortality rate within 90 days is 35.5% [2].Globally, approximately 1.2 million children and 3 million newborns are diagnosed with sepsis every year[3]. In my country, childhood sepsis also has the characteristics of high morbidity and mortality. Sepsis is an important disease of critically ill children in the PICU. Due to its high morbidity, high mortality, poor prognosis and the existence of the so-called "post-septic syndrome"[4], sepsis has always been a heavy burden on the country and the people. Over the past three decades, people have been looking for better and newer drugs to improve the high mortality of sepsis. For this reason, many clinical trials have been conducted, but all ended in failure[5]. Therefore, there is an urgent need to develop safe, effective and cost-effective medications for the treatment of sepsis. Studies have shown that in addition to conventional and basic treatment, vitamin C seems to show a certain therapeutic effect.

Sepsis and vitamin C deficiency:

The occurrence of sepsis involves a variety of pathophysiological mechanisms and the activation of multiple systems. With the continuous advancement of science, the immune imbalance, the intestinal flora imbalance, the consumption of coagulation factors, etc. have been put forward one after another. Inflammation seems to be a big part of it. When sepsis occurs, pro-inflammatory factors are excessively released to form an inflammatory storm, leading to tissue and organ dysfunction, and then anti-inflammatory factors increase through negative feedback expression to inhibit the release of pro-inflammatory factors and reduce cell tissue damage. However, too much pro-inflammatory factors are also harmful, and their excessive activation inhibits the immune system, leading to secondary infections in the late stage of sepsis, and the condition accelerates.

Oxidative stress acts as a regulator for systemic inflammation. Studies such as PARK have found that various pathophysiological mechanisms of sepsis are related to oxidative stress[6]. Oxidative stress will increase metabolic consumption in the body and reduce the circulation of oxidized vitamin C. Studies have shown that vitamin C in patients with sepsis is significantly reduced, which can be said to be in a state of deficiency, especially in patients with severe sepsis and patients with septic shock [7]. Therefore, the response to sepsis requires anti-inflammatory and oxidative stress. And exogenous vitamin C supplementation may be an effective auxiliary treatment measure.

The mechanism of action of vitamin C:

Vitamin C, also called ascorbic acid, is a water-soluble antioxidant and a variety of enzyme cofactors, which can prevent the adhesion of monocytes in endothelial cells and reduce inflammation. It participates in

many kinds of body redox reactions and may participate in the treatment of sepsis through the following effects:

Antioxidant effect:

During sepsis, the body generates a large amount of reactive oxygen species (ROS), which can cause irreversible damage to proteins, phospholipids, and nucleic acids[8]. Vitamin C has strong anti-oxidant characteristics. It can quickly eliminate it and other lipid peroxides after reacting with superoxide anions and oxygen free radicals, reducing the activity of tetrahydrobiopterin (BH4), and inhibiting reduced nicotinamide glands Purine dinucleotide phosphate (NADPH) oxidase (NOX) activity prevents ROS oxidative damage to proteins, lipids and DNA[9]. Wu et al studied vitamin C. They exposed skeletal muscle microvascular endothelial cells to lipopolysaccharides (LPs) in vitro. The study showed that pre-treated VitC can inhibit the expression of p47phox by inhibiting the Jak2/Statl/IRFl signaling pathway. NADPH oxidase is activated, ROS production is reduced, and endothelial cell oxidative damage is alleviated[10].Research by Yamazaki et al showed that the oxidative stress level of postoperative patients was significantly reduced after supplementing with 500 mg/d vitamin C for 3 consecutive days[11]. Dubick et al used a sheep burn model to study and found that the body's early fluid requirements were significantly reduced after the application of vitamin C, the plasma lipid peroxidation index was also significantly reduced, and the overall antioxidant status was maintained[12].

Anti-inflammatory effect:

The inflammatory storm of sepsis is closely related to the excessive production of nuclear factor kappa B (NF-κB). Anti-inflammatory balance disorder. Studies have shown that vitamin C can inhibit the activation of NF-κB by inhibiting the phosphorylation of inhibitory κ-B kinase (IKK) induced by tumor necrosis factor-α (TNF-α)[13]. Fisher et al studied a mouse model of sepsis and found that vitamin C-deficient mice significantly increased the synthesis of inflammatory mediators compared with vitamin C-sufficient mice, while the inflammatory response was attenuated after additional vitamin C supplementation, and found that additional vitamin C supplementation can reduce the gene expression and transcription of inflammatory mediators at the gene level[14]. Kang et al found that vitamin C inhibits the aggregation and adhesion of monocytes to endothelial cells by preventing the mRNA expression of IL-8 and MCP-1, thereby reducing the pro-inflammatory response[15]. Fowler et al used high-dose vitamin C to treat sepsis, and also demonstrated in a phase I clinical trial that the use of vitamin C can reduce the level of the pro-inflammatory biomarker C-reactive protein (CRP)[7].

Immunomodulatory effect:

As an important regulatory mediator in immunity, vitamin C may affect the proliferation and differentiation of a variety of immune cells, and plays an important role in improving the level of immune defense in the body. In the study of mice, Manning et al found that vitamin C played a role in promoting the proliferation and development of myeloblasts to functional T cells[16]. Some studies have also found that the proliferation of T cells was inhibited by vitamin C (500, 1 000 μmol/L) stimulation before human T cell activation or vitamin C (1 000 μmol/L) stimulation within 3h after T cell activation[17]. Studies have shown that

vitamin C can enhance the phagocytosis and killing ability of neutrophils, and promote the proliferation and differentiation of B cells and T cells[18]. Vitamin C can also enhance the ability of T natural killer (NK) cell progenitor cells to generate NK cell progenitor cells, and can promote the secretion of interleukin (IL) -12 from dendritic cells, thereby promoting the differentiation of naive $CD4^+$ T cells for helper T cells[19]. Gao et al found that in a mouse model of sepsis, after subcutaneous injection of 200 mg/kg vitamin C in mice, T cell-mediated immunosuppression was significantly reduced, the level of organ function was improved, and the incidence of dysfunction and mortality were also significantly drop[20].

Improve microcirculation and blood flow:

When sepsis occurs, pathogenic microorganisms and their released toxins can damage capillary endothelial cells, resulting in microcirculation disorders in sepsis, while vitamin C can protect endothelial cells. Mo et al studied human umbilical cord endothelial cells in vitro and found that vitamin C can prevent the formation of adhesion molecule 1(ICAM-1), thereby weakening leukocyte aggregation and correcting microcirculation[21]. Earlier studies have shown that vitamin C can protect capillary endothelial cells by altering the signal transduction pathway of capillary endothelial cells and inhibiting oxidative stress[22].

Another significant cause of microcirculation disturbance in sepsis is the formation of microthrombi. Swarbreck et al found that vitamin C can inhibit the production of plasminogen activator 1, thereby promoting the process of fibrinolysis and inhibiting the formation of microthrombi[23]. Studies have shown that vitamin C can reduce the aggregation and adhesion between platelets and endothelial cells by inhibiting the expression of P-selection (a key molecule for platelet endothelial cell adhesion), dredging capillary impaction, and dissolving microthrombi[24].The experiments of Secor et al also confirmed the inhibitory effect of vitamin C on platelets[25].

Vitamin C can also improve the state of microcirculation blood flow by inhibiting the constriction of arterioles[26] and restoring the compliance of arterioles.

The effectiveness of using vitamin C:

Protect the function of organs:

Patients with sepsis are often accompanied by multiple organ failure in the later stage, which is the main cause of death and poor prognosis of patients. Vitamin C works through the above mechanisms, and theoretically, it can improve organ failure to a certain extent. In 2014, Fowler et al conducted a randomized controlled study of 24 patients with severe sepsis from the ICU, and found that compared with the control group, patients receiving an intravenous vitamin C had a significantly lower degree of multiple organ failure[7]. In an analysis of 595 critically ill surgical patients, Nathens et al found that patients who received early enteral vitamin E and vitamin C supplementation had a decreased probability of multiple organ failure, and decreased mechanical ventilation time and ICU stay[27].

Vitamin C has been shown to protect multiple organ functions. Fisher et al found in a mouse model of acute lung injury caused by sepsis that after intraperitoneal injection of 200 mg/kg vitamin C, the release of inflammatory mediators in the alveoli of mice was cut, the inflammatory reaction was subdued, and the skeletal

construction of the alveolar epithelial cells was intact recovered and the lung function improved[28, 29]. Sepsis also often results in abnormal renal function. Giusti-paiva and other studies have shown that plasma vasopressin in mice is significantly increased after vitamin C injection[30], and vasopressin has been found to not only greatly change the hypotensive state of patients with sepsis, but also increase renal excretion, Reduced renal injury, decreased renal replacement therapy and use of catecholamines [31]. Vitamin C has also been found to have a protective effect on liver function. Kim et al. studied in septic rats and found that after the injection of vitamin C combined with vitamin E, the damage of cytochrome P450 in the liver of rats was reduced, the metabolism of the liver was improved, and the excessive oxidative stress and lipid peroxidation were significantly reduced. The hepatic inflammatory response is significantly reduced, and it can also improve the impairment of hepatic drug metabolism caused by abnormal cytochrome enzyme (CYP) family [32, 33].

Reduce mortality and improve prognosis:

Sepsis has become a heavy burden to countries and people because of its high mortality rate and poor prognosis. How to solve this problem has always been the focus of attention. Zabet et al conducted a randomized double-blind trial in 28 adult surgical septic shock patients and found that the 28-day mortality in the ascorbic acid group was significantly lower than that in the placebo group after vitamin C supplementation for 3 consecutive days (25 mg/kg, 4 times a day)[34].Li et al also used a meta-analysis to prove that the application of vitamin C can significantly reduce the mortality of patients with sepsis[35]. Shi-Jin et al conducted a randomized controlled study of 117 patients with sepsis. The control group was intravenously injected with 5% glucose and placebo (100 ml/time, twice a day), while the vitamin C group was intravenously injected with 3.0 g of vitamin C dissolved in 5% glucose (100ml/time, 2 times/day), after statistical analysis of mortality and efficacy, it was found that vitamin C can effectively improve organ function and reduce mortality in patients with sepsis[36].

Effectiveness of drug combination:

When used in combination with other drugs, vitamin C also showed a good therapeutic effect. In a study of ICU sepsis patients, Marik et al. conducted a study on ICU patients with sepsis and found that the risk of multiple organ failure and mortality were significantly reduced in patients who received simultaneous injection of vitamin C, hydrocortisone and vitamin B1, and the number of patients requiring renal replacement therapy was significantly lower than that of patients with sepsis who received neither vitamin C nor vitamin B1[37]. Studies have also confirmed that in children with early sepsis, after vitamin C combined with vitamin B1 and hydrocortisone treatment, the probability of acute kidney injury in children is greatly reduced, and oxidative stress and inflammatory stimulation are also rapidly reduced. Organ function decline was improved and mortality was reduced[38].

CONCLUSION

Sepsis is a serious threat to people's life and health, but the current treatment plan does not fundamentally solve the pathogenesis of sepsis, so it is imminent to seek new therapeutic drugs. Several studies

have shown that vitamin C can improve the physiological state of sepsis patients, inhibit organ failure, reduce mortality and improve prognosis through various mechanisms. However, some studies have shown that vitamin C treatment has not shown a therapeutic effect in patients with sepsis, so vitamin C treatment of sepsis is controversial[39].The《2020 Rescue Sepsis Campaign Guidelines》also do not recommend the light use of vitamin C in clinical treatment. It is worth noting that vitamin C is finally metabolized into oxalate in the body and excreted in the form of urine. Therefore, long-term use of large doses of vitamin C may form calcium oxalate stones in the kidneys. Patients with abnormal renal function should be cautious when using vitamin C. But the effect of vitamin C use cannot be denied. However, many problems are waiting to be solved, such as the optimal use time of vitamin C, the appropriate dose of vitamin C, and the safety of long-term high-dose use. Therefore, more, higher-quality, more convincing research and clinical trials are needed to solve these confusions and make people more convinced of the existing evidence, so as to achieve better results in the treatment of sepsis and increase people's happiness index.

REFERENCES

1. Singer, M., et al., *The Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3)* [J]. JAMA, 2016. **315**(8): p. 801-10.
2. Xie, J., et al., *The Epidemiology of Sepsis in Chinese ICUs: A National Cross-Sectional Survey*[J]. Critical care medicine, 2020. **48**(3): p. e209-e218.
3. Fleischmann-Struzek, C., et al., *The global burden of paediatric and neonatal sepsis: a systematic review*[J]. The Lancet. Respiratory medicine, 2018. **6**(3): p. 223-230.
4. van der Slikke, E., et al., *Exploring the pathophysiology of post-sepsis syndrome to identify therapeutic opportunities*[J]. EBioMedicine, 2020. **61**: p. 103044.
5. Artenstein, A., T. Higgins, and S. Opal, *Sepsis and scientific revolutions*[J]. Critical care medicine, 2013. **41**(12): p. 2770-2.
6. Park, D. and J. Zmijewski, *Mitochondrial Dysfunction and Immune Cell Metabolism in Sepsis*[J]. Infection & chemotherapy, 2017. **49**(1): p. 10-21.
7. Fowler, A., et al., *Phase I safety trial of intravenous ascorbic acid in patients with severe sepsis*[J]. Journal of translational medicine, 2014. **12**: p. 32.
8. Oudemans-van Straaten, H., A. Spoelstra-de Man, and M. de Waard, *Vitamin C revisited*[J]. Critical care (London, England), 2014. **18**(4): p. 460.
9. Wilson, J., *Evaluation of vitamin C for adjuvant sepsis therapy*[J]. Antioxidants & redox signaling, 2013. **19**(17): p. 2129-40.
10. Wu, F., et al., *Ascorbate inhibits NADPH oxidase subunit p47phox expression in microvascular endothelial cells*[J]. Free radical biology & medicine, 2007. **42**(1): p. 124-31.

11. Yamazaki, E., M. Horikawa, and R. Fukushima, *Vitamin C supplementation in patients receiving peripheral parenteral nutrition after gastrointestinal surgery*[J]. Nutrition (Burbank, Los Angeles County, Calif.), 2011. **27**(4): p. 435-9.
12. Dubick, M., et al., *High-dose vitamin C infusion reduces fluid requirements in the resuscitation of burn-injured sheep*[J]. Shock (Augusta, Ga.), 2005. **24**(2): p. 139-44.
13. Cárcamo, J., et al., *Vitamin C suppresses TNF alpha-induced NF kappa B activation by inhibiting I kappa B alpha phosphorylation*[J]. Biochemistry, 2002. **41**(43): p. 12995-3002.
14. Fisher, B., et al., *Attenuation of sepsis-induced organ injury in mice by vitamin C*[J]. JPEN. Journal of parenteral and enteral nutrition, 2014. **38**(7): p. 825-39.
15. Kang, J., et al., *Regulation of UVB-induced IL-8 and MCP-1 production in skin keratinocytes by increasing vitamin C uptake via the redistribution of SVCT-1 from the cytosol to the membrane*[J]. The Journal of investigative dermatology, 2007. **127**(3): p. 698-706.
16. Manning, J., et al., *Vitamin C promotes maturation of T-cells*[J]. Antioxidants & redox signaling, 2013. **19**(17): p. 2054-67.
17. Hong, J., et al., *Vitamin C is taken up by human T cells via sodium-dependent vitamin C transporter 2 (SVCT2) and exerts inhibitory effects on the activation of these cells in vitro*[J]. Anatomy & cell biology, 2016. **49**(2): p. 88-98.
18. Berger, M. and H. Oudemans-van Straaten, *Vitamin C supplementation in the critically ill patient*[J]. Current opinion in clinical nutrition and metabolic care, 2015. **18**(2): p. 193-201.
19. Mohammed, B., et al., *Vitamin C: a novel regulator of neutrophil extracellular trap formation*[J]. Nutrients, 2013. **5**(8): p. 3131-51.
20. Gao, Y., et al., *The Parenteral Vitamin C Improves Sepsis and Sepsis-Induced Multiple Organ Dysfunction Syndrome via Preventing Cellular Immunosuppression*[J]. Mediators of inflammation, 2017. **2017**: p. 4024672.
21. Mo, S., et al., *Modulation of TNF-alpha-induced ICAM-1 expression, NO and H2O2 production by alginate, allicin and ascorbic acid in human endothelial cells*[J]. Archives of pharmacal research, 2003. **26**(3): p. 244-51.
22. Wilson, J. and F. Wu, *Vitamin C in sepsis*[J]. Sub-cellular biochemistry, 2012. **56**: p. 67-83.
23. Swarbreck, S., et al., *Effect of ascorbate on plasminogen activator inhibitor-1 expression and release from platelets and endothelial cells in an in-vitro model of sepsis*[J]. Blood coagulation & fibrinolysis : an international journal in haemostasis and thrombosis, 2015. **26**(4): p. 436-42.
24. Tyml, K., *Vitamin C and Microvascular Dysfunction in Systemic Inflammation*[J]. Antioxidants (Basel, Switzerland), 2017. **6**(3).
25. Secor, D., et al., *Ascorbate inhibits platelet-endothelial adhesion in an in-vitro model of sepsis via reduced endothelial surface P-selectin expression*[J]. Blood coagulation & fibrinolysis : an international journal in haemostasis and thrombosis, 2017. **28**(1): p. 28-33.

26. Wu, F., J. Wilson, and K. Tyml, *Ascorbate protects against impaired arteriolar constriction in sepsis by inhibiting inducible nitric oxide synthase expression*[J]. Free radical biology & medicine, 2004. **37**(8): p. 1282-9.
27. Nathens, A., et al., *Randomized, prospective trial of antioxidant supplementation in critically ill surgical patients*[J]. Annals of surgery, 2002. **236**(6): p. 814-22.
28. Fisher, B., et al., *Ascorbic acid attenuates lipopolysaccharide-induced acute lung injury*[J]. Critical care medicine, 2011. **39**(6): p. 1454-60.
29. Fisher, B., et al., *Mechanisms of attenuation of abdominal sepsis induced acute lung injury by ascorbic acid*[J]. American journal of physiology. Lung cellular and molecular physiology, 2012. **303**(1): p. L20-32.
30. Giusti-Paiva, A. and V. Domingues, *Centrally administered ascorbic acid induces antidiuresis, natriuresis and neurohypophyseal hormone release in rats*[J]. Neuro endocrinology letters, 2010. **31**(1): p. 87-91.
31. Mogyorosi, A., *Vasopressin in septic shock*[J]. The New England journal of medicine, 2008. **358**(25): p. 2737; author reply 2737-8.
32. Kim, J. and S. Lee, *Vitamins C and E protect hepatic cytochrome P450 dysfunction induced by polymicrobial sepsis*[J]. European journal of pharmacology, 2006. **534**: p. 202-9.
33. Kim, J. and S. Lee, *Effect of ascorbic acid on hepatic vasoregulatory gene expression during polymicrobial sepsis*[J]. Life sciences, 2004. **75**(16): p. 2015-26.
34. Zabet, M., et al., *Effect of high-dose Ascorbic acid on vasopressor's requirement in septic shock*[J]. Journal of research in pharmacy practice, 2016. **5**(2): p. 94-100.
35. Li, J., *Evidence is stronger than you think: a meta-analysis of vitamin C use in patients with sepsis*[J]. Critical care (London, England), 2018. **22**(1): p. 258.
36. Lv, S., et al., *Early use of high-dose vitamin C is beneficial in treatment of sepsis*[J]. Irish journal of medical science, 2021. **190**(3): p. 1183-1188.
37. Marik, P., et al., *Hydrocortisone, Vitamin C, and Thiamine for the Treatment of Severe Sepsis and Septic Shock: A Retrospective Before-After Study*[J]. Chest, 2017. **151**(6): p. 1229-1238.
38. **于鑫岩**, *维生素C联合氢化可的松及维生素B1在脓毒症早期的临床研究*[J]. **世界最新医学信息文摘**, 2019. **19**(81): p. 156-157.
39. Teng, J., A. Pourmand, and M. Mazer-Amirshahi, *Vitamin C: The next step in sepsis management?* Journal of critical care, 2018. **43**: p. 230-234.