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# Is Vitamin C or HAT Therapy Effective in Treating Sepsis? A Mini Review

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**Received:** 22 August 2019 **Accepted:** 11 Febrary 2020
Published 2020 Volume 1, Issue 2,

**ABSTRACT**

**Background:** One of the most common causes of mortality in critical patients admitted to the intensive care unit (ICU) is sepsis. In recent years, the administration of high doses of vitamin C and HAT (hydrocortisone, ascorbic acid and thiamine) therapy has attracted much attention in patients with sepsis.

**Objectives:** The current article reviews the beneficial effects of HAT therapy in light of research conducted in this area.

**Methods:** A general search for electronic databases was developed. The human studies of the influence of HAT therapy in critically ill patients were evaluated.

**Results:** The results indicated that HAT therapy may improve clinical outcome in septic patients; however, widespread use of these therapeutic approaches in sepsis requires large clinical trials in order to more confidently recommend this therapeutic approach in septic patients admitted to intensive care units.

**Conclusions:** HAT therapy may improve clinical outcome in septic critically ill patients.

**Keywords:** Vitamin C, Hydrocortisone, Thiamine, HAT Therapy, Critical Ill Patients, Intensive Care Unit

**How to Cite:** Amini K, Sahebnasagh A, Mojtahedzadeh M. Is Vitamin C or HAT Therapy Effective in Treating Sepsis? A Mini Review. Critical Comments in Biomedicine. 2020; 1(2): e10018.

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## Introduction

Sepsis has been identified as an infection-induced systemic inflammatory response syndrome (SIRS) that causes lots of mortalities. Despite significant advances in the field of medicine and intensive care, a large study, reviewing national data of US, during 21 years, showed a 8.7 percent increase in sepsis incidence *[1]*. Sepsis is a life-limiting illness and one of the most common causes of mortality in intensive care units. In the United States, 750,000 new cases of sepsis are diagnosed each year *[2]*. In spite of many medical advances, it is estimated that more than 6 million people die each year due to sepsis, globally *[3]*. However, due to different definitions, reported events and mortality from sepsis, severe sepsis, and septic shock are highly variable and are likely to be less estimated .*[4]*

Current therapeutic approaches for sepsis include the use of wide-spectrum antibiotics, fluid administration, and vasopressors. However, the consequences and complications of treatment are high, indicating that such therapies do not have complete success rate *[5]*. Studies have shown that free radicals produced by peroxidation of lipids, nucleic acids and proteins are involved in many diseases *[6]*. This stress is caused by the imbalance between antioxidant defense systems and the production of free radicals and reactive oxygen

Published online: March 2020

species. There are some evidence that oxidative stress plays a potential role in the development of more than one hundred different diseases *[7]*.

Since patients with sepsis are exposed to a high load of oxidative stress, treatment with antioxidants as a therapeutic approach has been proposed *[8]*. For decades, antioxidants have been described as adjuvant therapy in critically ill patients and have been used extensively for the recovery of immunodeficiency in severe diseases *[9]*. Organisms need a variety of antioxidants to protect themselves against reactive oxygen species. Given the high load of oxidative stress in sepsis, we decided to investigate the role of vitamin C and hydrocortisone, ascorbic acid and thiamine (HAT) therapy in sepsis.

**Vitamin C and Sepsis**

Vitamin C (ascorbic acid) was introduced in the 1920s. It has been recommended for the treatment of several diseases. Because humans and some animals are unable to synthesize their own vitamin C in the liver, they need external vitamin C. In critical patients, vitamin C levels are greatly reduced *[10]*. Vitamin C (ascorbic acid) is a water-soluble molecule with pleiotropic functions. It is an essential antioxidant and has well-known anti-inflammatory and immune-enhancing properties *[10]*. Vitamin C is a cofactor for biosynthesis of collagen, catecholamines, vasopressors and other peptide hormones *[11]* and is essential in stress response by increasing cortisol and norepinephrine synthesis and recovering receptor sensitivity *[12, 13]*. Sepstic patients have lower levels of vitamin C due to decreased absorption and increased metabolism and redistribution of vitamin C *[14]*.

Human cells contain two important water-soluble antioxidants, vitamin C and glutathione tripeptide. Vitamin C plays an important physiological role in cells as a reductant and antioxidant, a free radical scavenger, and an enzymatic cofactor *[15, 16]*. Studies have shown that acute intravenous administration of vitamin C improves endothelial function in patients with type II diabetes *[17]*. It is estimated that sepsis patients have significantly lower serum levels of vitamin C, which can be corrected only by its intravenous administration at doses above 3 mg *[17, 18]*. Several studies have been done evaluating the effect of vitamin C on sepsis in vitro and clinical settings. The beneficial role of vitamin C in endothelial growth, survival, and its ability to maintain vascular responsiveness and integrity has been demonstrated *[19]*. A study using the human umbilical endothelial cell line has shown that vitamin C can prevent the increase in α-TNF-induced inflammation in intercellular adhesion molecule-1 (ICAM-1) *[20]*. The role of corticosteroids in enhancing vitamin C uptake has been shown and it has been found to restore glucocorticoid receptor function *[21, 22]*. Animal studies have shown that vitamin C is able to reduce metabolic, pro-inflammatory and pro-coagulant changes *[23]* and increase urine output *[24]*. Some clinical trials have shown beneficial effects of vitamin C in patients with sepsis after surgery or major trauma, but all studies have not yielded positive results *[25]*. The differences in results of these studies might be due to changes in timing, dosage and route of administration, since direct radical scavenging of vitamin C depends on plasma concentrations above 175 mg/L *[26]*. Oral administration of this supplement cannot increase plasma concentrations to this level, because the rate of internal absorption in sepsis patients is very limited and sometimes impaired *[26]*. Recently, three small studies using pharmacological doses have raised interest in the administration of vitamin C in patients with sepsis. In these studies, patients receiving intravascular vitamin C at a dose of 50 to 200 mg/kg/day showed reduced rate of organ failure *[23]* and 28-day mortality *[17]* depending on the dose used. Beneficial effects of vitamin C and E administration on pulmonary morbidity and organ failure were observed in 595 critical patients admitted to the intensive care unit (ICU). The administration of these vitamins also reduced the length of stay in the ICU and the incidence of organ failure *[27]*. Results of a double-blind clinical trial indicated that administration of vitamin C to patients with septic shock significantly reduced the needed doses of

vasopressors *[28]*. A significant reduction in mortality and mortality in septic shock patients was observed in administration of vitamin C along with thiamine and hydrocortisone *[29]*.

Although the beneficial effects of vitamin C in sepsis patients have been reported in trials, high-dose vitamin C administration can have adverse effects on patients. Renal failure, deficiency of glucose-6-phosphate dehydrogenase, calcium oxalate nephropathy has been reported *[30]*. Also, due to the structural similarity between ascorbic acid and glucose, point-of-care blood glucose measurements after vitamin C injection may be inaccurate and the results should be interpreted with caution *[31]*.

**HAT Therapy for Sepsis**

Improved oxygen delivery through a variety of interventions such as the administration of fluids and vasoactive drugs in patients with sepsis and septic shock is now widely used. The combination of corticosteroids, ascorbic acid and thiamine in recent years has attracted much attention in the treatment of these patients. The beneficial effects of the combination of hydrocortisone, ascorbic acid, and thiamine (HAT) in critically ill patients admitted to ICU with severe pneumonia have been shown in a recent study and led to a reduction in mortality in these patients *[32]*. Since 2016, the combination of these drugs has been considered in patients with sepsis *[33, 34]*. The results of studies using the combination of hydrocortisone, ascorbic acid, and thiamine in the routine management of sepsis have been inconsistent and some have been supported *[35]* and some have suggested require further investigation *[36]*.

The advantages of HAT treatment include low risk and relatively low cost of intervention. However, this combination treatment also has disadvantages, such as long-term intervention, and lack of safety profile of high dose vitamin D in these patients. However, because large and comprehensive studies in this field are so scarce, the generalization of the results of observational studies has raised concerns. In this context, randomized clinical trials are needed to evaluate the effect of HAT treatment on important clinical outcomes in patients with sepsis. Although HAT seems to be a promising treatment for sepsis resuscitation, there is currently no strong evidence to support its widespread use. The efficacy of this combination drugs is assessed in the observational data and further studies are currently needed *[37-41]*.

**Conclusion**

According to studies regarding the effect of vitamin C alone and in combination with hydrocortisone and thiamine in sepsis patients it can be said that high-dose vitamin C might have protective effects against oxidative stress induced organ failure in patients with sepsis. However, further studies are needed to determine the appropriate dose, administration timing and associated side effects.

**Acknowledgments**

The authors gratefully acknowledge the hard-working staff of Sina Hospital of Tehran University of Medical Sciences.

**Funding source**

None

**Authors' contribution**

KA Carried out a literature search and prepared the primary draft. AS prepared the final manuscript and edited the English manuscript. MM Generated the idea of the manuscript and had a scientific supervision.

**Conflict of interest**

No competing financial or other interests exist.

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