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The vitamin C, thiamine and steroids (VICTAS) in sepsis

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ABSTRACT

Sepsis is organ failure caused by an infection. It is one of the leading causes of in-hospital mortality worldwide. Standard treatment uses broad-spectrum antibiotics, fluid resuscitation, and vasopressor support in resistant hypotensive patients. Nevertheless, high morbidity and mortality rates in severe sepsis and septic shock have led to the search for new treatment modalities. In this review, we discuss the effects of intravenous ascorbic acid (vitamin C), thiamine (vitamin B1) and steroid treatment in addition to standard treatment in patients with severe sepsis and septic shock.

Keywords: Ascorbic acid, sepsis, septic shock, steroid, thiamine, VICTAS.

AN OVERVIEW OF SEPSIS AND SEPTIC SHOCK CONCEPTS

Sepsis is the development of severe organ failure as a result of the dysregulated response of the patient organism due to any infection. Patient creates an abnormal inflammatory response against the infection physiologically, biologically and biochemically, and this response causes organ failure by creating tissue damage rapidly. More than 30 million individuals around the world have sepsis each year, and sepsis is the main cause of one-third of the in-hospital mortality.[1]

Patients with high risk factors for sepsis are hospitalized, had a long hospitalization period, elderly, pregnant or newborn patients, organ failure, particularly liver, immunosuppressed due to chemotherapy or steroid use, and patients with autoimmune diseases.[1] The patient in the diagnosis of sepsis evaluated as respiratory, cardiovascular, hepatic, hematological, renal and neurological. As a result of all these evaluations, a final score is obtained with the Sepsis-Related Organ Failure Assessment (SOFA) scoring. Each item gets a score between 0 and 4 as the total score is between 0 to 24. High scores correlate with high mortality rates (Table 1).[2]

Dysregulated host response in sepsis leads to leakage from the vessels and hypotension due to tissue damage following the activation of proinflammatory mediators.[3] Development of hyperthermia or hypothermia in the organism, increase of C-reactive protein (CRP), increase of procalcitonin (PCT) in plasma, hyperglycemia, increase in lactate level, hypotension, tachycardia and tachypnea are among the markers of sepsis.[1] Current treatments focus on early detection of sepsis and then the use of broad-spectrum antibiotics and supportive therapy to optimize oxygen supply. In addition, it is recommended to give fluid to the patient and to start a vasopressor in resistant hypotension.[3] Although the results have improved with the combination of these strategies,[4-7] the mortality rate remains high, with rates of 20 to 30%.[8,9] Survivors experience significant decreases in their physical, emotional, and cognitive quality of life.[10,11] Low-cost and low-risk therapeutic approaches are needed to reduce sepsis morbidity and mortality.

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Table 1. SOFA score chart[1]

	1*	2	3	4
Respiratory PaO_2/FiO_2 mmHg	≤400 MV yes/no	≤300 MV yes/no	≤200 MV yes	≤100 MV yes
Cardiovascular Hypotension	MAP <70 mmHg	Dopamine ≤5 and Dobutamine*	Dopamine >5 or adrenaline ≤0.1 or noradrenaline ≤0.1**	Dopamine ≥15 or adrenaline >0.1 or noradrenaline >0.1**
Liver Bilirubin mg/dL	1.2-1.9	2.0-5.9	6.0-11.9	>12
Coagulation Platelets 10^3 mm^3	≤150	≤100	≤50	≤20
Kidney Creatinine mg/dL or urine flow	1.2-1.9	2.0-3.4	3.5-4.9 flow ≤500 mL/day	>5 flow ≤200 mL/day
Neurologic Glasgow Coma Score	13-14	10-12	6-9	<6

* Values beyond this limit get zero points; ** It should be given at a dose of µg/kg/min for at least 1 h; MV: Mechanical ventilation; MAP: Mean arterial pressure.

Septic shock is defined as resistant hypotension requiring vasopressor therapy and serum lactate levels above 2 mmol/L, despite adequate fluid resuscitation.[1] New treatment options focusing on alleviating the erratic host response in sepsis and septic shock and reducing the need for vasopressors or the duration of use are under investigation. Patients with high vasopressor need have high mortality rates.[12] Although many studies have been conducted on the use of ascorbic acid (vitamin C), thiamine (vitamin B1) and steroids alone or in triple combination in the treatment of sepsis and septic shock,[13-23] further studies are needed to determine the most effective doses and periods of use. These therapies can work synergistically and reverse the pathophysiological changes in sepsis with mechanisms such as presenting anti-inflammatory effects, nitric oxide production, catecholamine production, increased vasopressor sensitivity, and blood pressure regulation.[15,24-26] In this review, we investigate clinical trials related to the specialized name The Vitamin C, Thiamine and Steroids in Sepsis (VICTAS) Protocol, together with the studies on the combined use of vitamin C, thiamine, and steroids in the treatment of sepsis and septic shock.

ASCORBIC ACID (VITAMIN C)

Ascorbic acid is a water-soluble essential vitamin which cannot be synthesized by the human body. It is a well-known antioxidant, as it is a direct purifier of free radicals.[27] It works as a cofactor for iron and copper-containing enzymes.[28,29] Due to the increased number of free radicals in sepsis, free iron is reduced by iron and folate metabolism. Ascorbic acid, which acts as an electron donor in the reduction of iron, is extremely depleted in the case of sepsis where free radicals are intensely increased.[30]

Ascorbic acid has anti-inflammatory effects and increases nitric oxide production and vasopressor sensitivity.[24,25] In addition, it can increase catecholamine and cortisol synthesis in the adrenal medulla and protect the integrity of the endothelium.[14,23,31] Ascorbic acid protects vascular endothelial function and microcirculatory flow by activating the nuclear factor erythroid 2-like (Nrf2) "2/heme oxygenase 1" pathway, which regulates the activities of antioxidants, T-cells and macrophages.[32,33] For many years, it has been observed that critically ill patients, including sepsis patients, routinely have very low plasma vitamin C concentrations (<15 µmol/L).[34-36] Although circulating vitamin C concentrations reflect adherence to recommended dietary intake (~50 µmol/L),[37] activation of complement-mediated inflammation can lead to insufficient intracellular concentrations.[38] Intravenous (IV) vitamin C supplementation of sepsis in animal models increased arteriolar response to vasoconstrictors and capillary blood flow and decreased microvascular permeability and organ dysfunction.[24,25,39] In lung injury models, vitamin C improved epithelial barrier function, alveolar fluid clearance, weakened microvascular coagulation abnormalities and

thrombosis in the lung.[40] In a study of patients with sepsis, proinflammatory markers such as thrombomodulin, which is a measure of endothelial damage, were found to be lower in patients receiving IV vitamin C.[13] In another phase study examining patients with vasopressor-dependent sepsis, norepinephrine dose-duration and patient mortality were significantly lower in patients receiving high-dose IV vitamin C.[14] Ascorbic acid at physiological pH turns into sodium ascorbic, the mineral salt and form of ascorbic acid found in cells. It has been suggested that the infection induces endogenous ascorbate depletion during sepsis.[13,36,41] Depletion of ascorbic acid is associated with decreased norepinephrine levels, which are often seen in critically ill patients, leading to insufficient synthesis of adrenal hormones.[14] Recent studies have revealed that administration of high-dose IV ascorbic acid can reduce organ damage and vasopressor need and increase the survival rate in sepsis and septic shock.[14,23]

In a recent large-scale, observational study, neurological dysfunction was found to be the most closely related to early and late mortality in patients with sepsis.[42] Therefore, interventions with potentially neuroprotective effects are also very interesting. Vitamin C is a therapy with high potential due to its antioxidant properties and effects on both the endothelium and the blood-brain barrier. In an animal model of sepsis, treatment with antioxidants was shown to prevent the development of cognitive deficits for 30 days.[43] In addition, lower concentrations of vitamin C in the plasma and cerebrospinal fluid of patients with sepsis increased the risk of encephalopathy and the permeability of the blood-brain barrier.[44,45]

In 2014, a Phase I trial was conducted to evaluate the efficacy and safety of ascorbic acid in patients with severe sepsis. This was a small-scale, double-blind, randomized, placebo-controlled study involving 24 patients with severe sepsis.[13] The main objectives were to determine whether IV ascorbic acid was safe for use in critically ill patients with severe sepsis and to determine whether ascorbic acid had an effect on organ failure. In this study, IV ascorbic acid was administrated at 50 or 200 mg/kg/day (four equal doses, q6h, for 30 min, as an infusion for a total of 96 h) and the effect of ascorbic acid was observed by measuring the blood plasma biomarkers such as CRP, PCT, and thrombomodulin levels and calculating SOFA scores. Both doses have been lower SOFA scores over the four-day study period, with a greater decrease with higher doses ($p<0.01$).[13] Also, CRP and PCT levels were significantly decreased, compared to placebo. Thus, IV ascorbic acid is safe to administer in critically ill sepsis patients, may lead to a greater decrease in SOFA scores, and improve proinflammatory markers in sepsis.[13]

In 2016, another pilot study was conducted to evaluate the effect of high-dose ascorbic acid on vasopressor dose and duration. In this randomized, double-blind, placebo-controlled clinical trial conducted with 28 patients diagnosed with septic shock requiring vasopressors; ascorbic acid was administered as 25 mg/kg IV, q6h, for 30 min over 72 h.[14] This high-dose ascorbic acid significantly reduced the required dose and duration of vasopressor in patients with septic shock compared to placebo and improved norepinephrine levels in the first 24 h.[14] The results show that high-dose ascorbic acid (25 mg/kg IV, q6h, for 72 h) can be evaluated as an effective and safe adjuvant therapy in critically ill patients with septic shock. Limitations of the study include small sample size, short study duration, and lack of measurement of basal serum ascorbic acid levels. Although both studies conducted in 2014 and 2016 show positive results in terms of safety and effectiveness, more research is needed for the most effective ascorbic acid dose and application.

Although vitamin C therapy was safe in a small sample study conducted by Fowler et al.[13] with all the beneficial effects revealed by ascorbic acid administration in sepsis and septic shock, the lack of appropriate safety studies at higher doses and sufficient sample sizes does not eliminate the concerns about safety. It is known that the use of vitamin C causes concerns about oxalate accumulation and increases the risk of kidney stones, particularly in patients with renal dysfunction.[46,47] Although there is no significant relationship between serum ascorbic acid level and the prevalence of kidney stones, administration at a dose of 2 g/day increases urinary oxalate levels.[46,47] However, Padayatty et al.[48] evaluated the adverse effects of high-dose IV ascorbic

acid in 9,328 patients and found that only one patient developed oxalate kidney stones and two unspecified kidney stones. One of the patients developed acute renal failure; however, it was observed that this patient was with a diagnosis of renal metastasis. In addition, there are concerns that high dose IV ascorbic acid may interfere with the accuracy of routine blood glucose level measurements.[49] The wide dosage ranges used in ascorbic acid trials, suitable dose finding studies and the lack of sufficient pharmacokinetic data create uncertainty in choosing the most appropriate dose.

Therefore, future studies should focus on determining the optimal dose, duration of treatment, and optimal form of therapy. In this respect, the results of the Ascorbic Acid Infusion (CITRUS-ALI) study in the treatment of acute lung injury from sepsis are awaited with curiosity.[1,50] In this study, ascorbic acid was administered as 200 mg/kg/day, divided into four daily doses for every 6 h for a total of 96 h and its effect was compared with placebo.[50] The primary outcomes are the change in SOFA scores, CRP, and thrombomodulin results. Although this was not exactly similar to the protocol conducted by Marik et al.,[23] this study would help highlight the efficacy in high-dose ascorbic acid administration, and more importantly, concerns about safety.

THIAMINE (VITAMIN B1)

Thiamine is an essential component of cellular metabolism. It is a water-soluble vitamin that protects tissue against oxidative damage.[26] Thiamine deficiency is common in septic shock and other critical disease conditions at rates varying between 20% and 70%.[26,51] It exists in the organism as free thiamine and other phosphorylated forms. Thiamine pyrophosphate is an active form that works as a catalyst in the conversion of pyruvate to acetyl-coenzyme A in the Krebs cycle for energy production.[52,53] Thiamine deficiency is common in critically ill patients and can lead to lactic acidosis as pyruvate cannot enter the Krebs cycle.[54]

Thiamine is also a coenzyme for transketolase, a cytosolic enzyme in the pentose phosphate pathway. This enzyme maintains cell redox status by reducing nicotinamide adenine dinucleotide phosphate and glutathione.[15] Therefore, thiamine is important in converting glucose into pyruvate for energy production.[52,53] In untreated thiamine deficiency high lactate can lead to aerobic metabolism deficiency, resulting in hypotension and death.[51] Supplementation of 200 mg IV thiamine for every 12 h significantly reduce lactate levels in critically ill patients with basal thiamine deficiency.[15]

Thiamine deficiency increases oxidative stress and cell damage by causing bioenergetic failure and accelerates organ failure, including neuronal injury and brain dysfunction.[50,55] Administration of thiamine to support the metabolism of patients with septic shock may be a smart approach due to acute consumption of thiamine in the hypermetabolic state of septic shock and its important roles in cellular metabolism.[56] The hypothesis of administering thiamine during septic and septic shock suggests that oxidative stress levels and mortality can be decreased in patients with septic shock.[15,26]

The use of IV thiamine was evaluated in a randomized, double-blind, placebo-controlled, pilot clinical trial in 2016. The study was carried out on vasopressor-dependent adult patients with persistent sepsis following more than 2 L of liquid bolus, lactate levels >3 mmoL/L and hypotension (systolic blood pressure <90 mmHg). Patients were randomized into those given 50 mg thiamine twice daily for seven days (n=43) and those given placebo (n=45). The mean age of the study population was 67 years and 41% of the patients were females. Lactate levels decreased in 24 h following thiamine administration.[15]

In 79 patients whose baseline thiamine levels were measured, thiamine deficiency was detected in 15 patients in the thiamine replacement group and 13 patients in the placebo group. Among thiamine-deficient patients, the study demonstrates the potential benefits of thiamine for the treatment of septic shock, particularly in patients with thiamine deficiency, as those in the thiamine group reached statistically significant lactate levels within 24 h ($p=0.303$).[15] More studies are needed to investigate these positive effects. Restrictions in the study is a single center patient registry that may limit the small sample size and generalizability of the results. It remains unclear whether the treatment effects of thiamine are time-dependent, as the maximum time for

enrollment is not specified in the study design. In addition, the dosage used in the study was based on previous doses that effectively counteracted the lactate elevation in other disease states and pure thiamine deficiency, although it was not based on any dose finding trials.[15]

A secondary analysis was conducted in 2017 to evaluate the hypothesis that thiamine supplementation could reduce kidney injury in septic shock. In the study conducted by Moskowitz et al.,[16] medical data of patients including baseline creatinine levels, the worst creatinine levels (3 to 24 h, 24 to 48 h, and 48 to 72 h), kidney function, need for renal replacement therapy (RRT), RRT indication, and timing of onset of RRT were obtained. There were 70 patients in the study with no significant difference in terms of basal creatinine levels between the thiamine and placebo groups. As study outcomes, more patients in the placebo group compared to the thiamine group needed RRT; acidosis was observed in six cases, five of them were found to be in the placebo group and one in the thiamine group. The average time from thiamine administration to the onset of RRT was calculated as 26 h. In the repeated measures analysis, the worst creatinine levels were found to be lower in the thiamine group than in the placebo group ($p=0.05$).[16] Although post-hoc analysis and the small sample size of this analysis may limit the validity and generalizability of the results, the study findings suggest a hypothesis for future research on a larger scale to determine the role of thiamine in sepsis-related renal dysfunction.

In a retrospective, single-center group study published in 2018, patients with high lactate levels and needing vasopressors were evaluated to determine whether thiamine administration in septic shock increased lactate clearance and whether these patients had other positive results compared to those who did not take thiamine.[17] Thiamine administration was performed by giving any dose of IV thiamine supplement within 24 h after hospitalization. The study consisted of 123 patients who received IV thiamine treatment and 245 patients who did not. Although multiple dosage regimens are used, the most common is 500 mg IV, q8h, for 72 h. The primary outcome is shortening duration for lactate clearance in septic shock and the secondary consequences are a decrease in 28-day mortality, acute kidney injury, the need for RRT, vasopressor and mechanical ventilation.[17] The mortality rate in patients receiving thiamine was lower than in the placebo group. Also, interestingly, sub analysis showed that females responded better to thiamine treatment in terms of lactate clearance and mortality than males. Since it is a retrospective study, thiamine dosage cannot be clearly evaluated in terms of safety results and side effect profiles.[17]

Thiamine administration may be particularly beneficial in patients with septic shock with thiamine deficiency by lowering lactate levels.[15] In addition, serum creatinine levels and the possibility of taking RRT were found to be lower in patients who received IV thiamine.[16] Woolum et al.[17] showed that administration of IV thiamine in the early period in septic shock increased lactate clearance and decreased mortality, particularly in females. It is assumed that the greater benefit in females is due to the increased risk of thiamine deficiency. Although thiamine is relatively non-toxic, severe hypersensitivity reactions are rarely possible after repeated parenteral administration.[57] Also, some thiamine formulations contain aluminum, which can accumulate in patients with kidney disease at levels associated with the central nervous system and bone toxicity. Since thiamine test results are effective in the long period, administration of thiamine may be considered in all patients during early septic shock, since thiamine administration does not cause serious problems in terms of both economic and safety. However, larger prospective clinical studies should be conducted to evaluate the safety, efficacy, dose and timing of administration.

CORTICOSTEROIDS

Corticosteroids regulate many physiological processes by their glucocorticoid and mineralocorticoid receptors. Glucocorticosteroids have been shown to reduce inflammation by activating glucocorticoid receptors.[58] Simultaneously, they regulate chemokinesis and phagocytosis processes and show antioxidant effects. They inhibit inflammation by inhibiting proinflammatory genes and inducing anti-inflammatory genes. Activation of mineralocorticoid receptors primarily enables sodium and water retention by increasing the expression of sodium

channels and Na/K/ATPases in the tubules collected in the kidneys.[59] In sepsis and septic shock, mineralocorticoid and glucocorticoid activation tries to regulate circulation while decreasing inflammatory processes.[3]

Hydrocortisone was first included in the Surviving Sepsis Campaign guidelines in 2004 and continues to be recommended in the 2016 update.[3] Despite fluid resuscitation and vasopressor therapy, the administration of hydrocortisone in patients with septic shock with hypotension is currently included in the standard of care.[3] The evidence for hydrocortisone in septic shock is increasing day by day; however, many of these are still in the theory stage. Glucocorticoids may inhibit the induction of nitric oxide synthase, an enzyme that causes relaxation of vascular smooth muscle, which can result in vasodilation and hypotension.[60] In vascular endothelial cells, they suppress the production of vasodilators such as prostacyclin and nitric oxide.[58] As an anti-inflammatory agent, hydrocortisone may be helpful in reducing maladaptive responses and relative adrenal insufficiency during septic shock.[61,62]

In 2002, a multi-center, randomized, double-blind, parallel group study was conducted by Annane et al.[18] and the aim of this study was to evaluate whether hydrocortisone plus fludrocortisone therapy improved 28-day survival, particularly in patients with septic shock with relative adrenal insufficiency. Relative adrenal insufficiency was defined as an increase in serum cortisol levels 9 mg/dL in response to an IV bolus 250 mg adrenocorticotropic hormone (ACTH). In the study with 300 septic shock patients requiring mechanical ventilation were evaluated and IV bolus hydrocortisone 50 mg, q6h, and fludrocortisone 50 mg tablet replacement once daily via a nasogastric tube containing 10 to 40 mL of water over 30 sec for seven days. The results were found to be statistically significant, and a decrease in 28-day mortality and vasopressor application time was shown in all patients with septic shock, particularly those with relative adrenal insufficiency.[18] These results confirm the hypothesis that patients with septic shock with relative adrenal insufficiency may have benefit from replacement therapy as a combination of hydrocortisone and fludrocortisone. According to the results of the ACTH test, it was concluded that the treatment could be withdrawn in those who responded to replacement and continued for up to seven days in those who did not respond.[18]

In the CORTICUS (Hydrocortisone Therapy for Patients with Septic Shock) study published in 2008, the use of corticosteroids was evaluated in more severe patients with sepsis.[19] In this multi-center, randomized, double-blind, placebo-controlled Phase III clinical trial, there were 499 patients with septic shock within the previous 72 h. Adrenocorticotropic hormone test was applied to all patients and they were classified as responders (cortisol increase >9 mg/dL) and non-responders (cortisol increase 9 mg/dL) by test. The primary outcome was to evaluate the 28-day mortality rate among patients who did not respond to ACTH after treatment with hydrocortisone as adjunct therapy. Hydrocortisone was administered as 50 mg IV bolus, q6h, for five days, then 50 mg IV, q12h, for six to eight days and finally 50 mg IV, q24h, for nine to 11 days. However, the findings reveal that there is no significant reduction in 28-day mortality in patients with septic shock.[19] It is thought that the criteria for the study of having a diagnosis of severe septic shock 72 h before the start of replacement may be too long for the potential for hydrocortisone to act.

In the HYPRESS (Hydrocortisone for Prevention of Septic Shock) study published in 2016, a randomized, double-blind, multi-center, placebo-controlled clinical trial was conducted. 380 patients with severe sepsis for less than 48 h; however, they are not yet in septic shock were evaluated and the development of septic shock within 14 days after administration of hydrocortisone as a primary outcome was evaluated. Hydrocortisone was initially administered as a 50 mg IV bolus followed by a continuous 24-h infusion of 200 mg; 100 mg on Days 5, 6, and 7; 50 mg on Days 8 and 9; and 25 mg infusion was carried out on Days 10 and 11. Therefore, no significant difference was found between the treatment group and the placebo group in the development of septic shock after 14 days.[20]

The ADRENAL (Adjunctive Corticosteroid Treatment in Critically Ill Patients with Septic Shock) study published in 2018 is a randomized,

double-blind, placebo-controlled, interventional Phase IV clinical study involving 3,800 patients with mechanical ventilation-dependent septic shock.[21] Hydrocortisone was administered as a continuous infusion IV at a rate of 200 mg/day for seven days. There was no significant difference in 90-day mortality between the treatment and placebo groups. However, similar to the CORTICUS study, shorter treatment in the intensive care unit (ICU) was sufficient with the lower incidence of transfusion and earlier cessation of mechanical ventilation in the hydrocortisone group.[21] Possible secondary infections and the appropriateness of antibiotic treatment could not be evaluated in this study.

In the APROCCHSS (Activated Protein C and Corticosteroids for Human Septic Shock) study published in 2018, a multi-center, double-blind, randomized, placebo-controlled, interventional Phase IV clinical trial was conducted involving 1,241 patients with septic shock.[18,22] The primary endpoint was 90-day mortality after administration of hydrocortisone plus fludrocortisone along with standard care. Safety results include up to 180 days of superinfection, up to 28 days of gastrointestinal (GI) hemorrhage, episodes of hyperglycemia up to seven days, and neurological sequelae examined in the ICU, at discharge, on Day 90, and on Day 180. Hydrocortisone was administered as 50 mg IV bolus, q6h, and one tablet of 50 mg fludrocortisone daily via nasogastric tube. On the 90th day, mortality was observed to be significantly lower in the treatment group (43%) than placebo (49%). Although the risks of GI hemorrhage and superinfection were not significantly higher in the treatment group compared to placebo and the risk of hyperglycemia was significantly higher in the treatment group.

As a result of these studies on steroid use, different results were obtained in terms of mortality benefits when additional steroids were used.[18-22] While CORTICUS and ADRENAL studies did not show a mortality benefit, both showed that septic shock was reversed more rapidly with hydrocortisone use.[19,21] The APROCCHSS study is the first large clinical trial to show a mortality benefit to steroid therapy, probably as it used fludrocortisone therapy in combination with hydrocortisone. In a smaller study conducted by Annane et al.,[18] in which hydrocortisone and fludrocortisone were administered in patients with septic shock, similar mortality benefits were shown in addition to shortening the duration of mechanical ventilation. Fludrocortisone can potentiate the benefits arising from its more potent mineralocorticoid activity, thus increasing blood pressure and reducing the need for vasopressor therapy.

TRIPLE COMBINATION THERAPY TRIALS (VICTAS) IN SEPSIS

The treatment regimen in which ascorbic acid (vitamin C), thiamine (vitamin B1) and steroid (hydrocortisone) replacements are applied in triple combination is called VICTAS. Marik et al.[23] conducted the first study in this area by retrospectively evaluating patients with a primary diagnosis of severe sepsis or septic shock. Patients under 18 years of age, pregnant or with care restrictions were excluded in the study.[23] In accordance with the intensive care protocol, all patients with sepsis and septic shock were empirically given broad-spectrum antibiotics; these were then reduced based on cultures and clinical progress and treated with fluid resuscitation and vasopressor support.[23] 50 mg, q6h, hydrocortisone was given to the patients in the control group, which was examined seven months before the triple therapy study, at the physician's discretion.[23] During treatment, patients should receive IV ascorbic acid (1.5 g, q6h, for four days or until they leave ICU), hydrocortisone (50 mg, q50h, for seven days or until they leave ICU) and IV thiamine (for four days, treated with 200 mg, q12h, or until they left the ICU (Figure 1). There are 47 patients in each group. Ascorbic acid levels were determined before the first ascorbic acid dose.[23]

There is no significant difference in basic characteristics between the study groups. However, in-hospital mortality decreased significantly in the VICTAS treatment group compared to the control group (8.5% vs 40.4%).[23] Progressive organ failure did not develop in any of the patients in the treatment group, and the duration of vasopressor use was significantly reduced.[23] One of the handicaps of the study is that the study was retrospective, single center, small sample size and the patients were evaluated in different time periods. In addition, the benefit

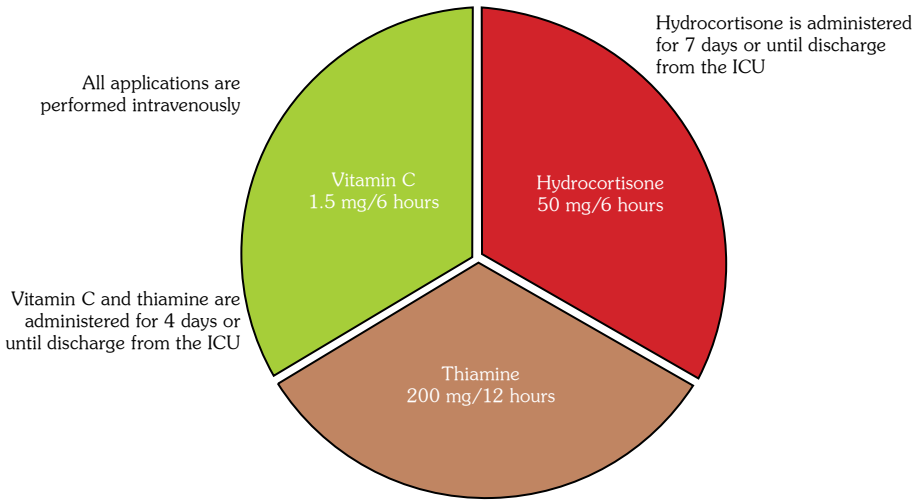

Figure 1. VICTAS protocol.
ICU: Intensive care unit.

of triple therapy may have been masked by the use of hydrocortisone in the control group. The administration of thiamine with high-dose IV ascorbic acid may prevent oxalate production due to ascorbic acid, thus reducing the risk of renal crystallization in patients with renal failure.[57,63,64] Although this study revealed positive results, larger randomized controlled trials should be conducted to investigate the benefits of triple therapy in addition to standard care in sepsis and septic shock. Although the use of IV ascorbic acid, thiamine, and hydrocortisone separately in critically ill patients has shown positive effects in the literature,[13-21] this study is the first to use them in combination for their synergistic effects.

Multi-center studies are currently being conducted to investigate the benefits of combination therapy in larger populations. In this context, with a multi-center study that would investigate the effects of VICTAS therapy on 2,000 patients[51] and the results of another blind and randomized study involving approximately 200 patients are awaited.[65] In the VICTAS study conducted by Hager et al.[66] patients with respiratory and cardiovascular disorders due to sepsis and who need vasopressor and ventilator support (VVFD) are evaluated. The protocols used include 1.5 g IV ascorbic acid, q6h, 100 mg IV thiamine, q6h, and 200 mg IV hydrocortisone daily, similar to those used by Marik et al.[23] The effectiveness of combined therapy is measured by its potential to reduce mortality and whether it cuts the need for VVFD. The VICTAS trial also produces data to measure the relationship between sepsis and neurocognitive functionality and the possible effects of combined therapy on short and long-term neurocognitive outcomes. Finally, the study is also important in characterizing the pharmacokinetics of vitamin C, measuring standard and new markers of generally emerging sepsis severity, and creating a bio-storage that would be used to determine high vitamin C concentrations.[66] In addition, it would be exciting to examine the effects of quadruple therapy (IV ascorbic acid, thiamine, hydrocortisone, and fludrocortisone) in patients with sepsis and septic shock, since the additional benefit of adding fludrocortisone to hydrocortisone as adjuvant therapy in patients with septic shock.[18-22]

However, the study published by Litwak et al.[67] in April 2019, examining the clinical results of triple combined therapy (vitamin C, thiamine and steroid) in case of severe sepsis and septic shock gives a different result from the findings of Marik et al.[23] In this retrospective, observational cohort study in which 94 patients were evaluated in two equal groups (triple therapy group n=47 and standard care group n=47), the primary outcome was that there was no significant difference in the in-hospital mortality rates (40.4%

vs 40.4%). In addition, no significant difference was found in secondary outcomes, including ICU mortality, need for RRT for acute kidney injury, duration in the ICU, duration of hospitalization, and time to cessation of vasopressor support. According to this study compared to standard care, triple combination therapy does not improve the in-hospital or ICU mortality in patients with septic shock.[67] These results were compatible with the study results of Shin et al.[68] In the retrospective studies of Shin et al.[68] on early triple combined therapy of patients with septic shock, early administration of vitamin C and thiamine did not cause mortality benefit in the general patient population; however, subgroup analysis demonstrated that its improved survival in patients with hypoalbuminemia (albumin <3.0) or severe organ failure (SOFA >10).

Litwak et al.[67] reported that their results differed from those of Marik et al.[23] by the fact that the triple therapy was not fully protocolized in their institution. A total of 27 (54%) of the patients in the triple therapy group did not receive triple combined therapy during the full treatment period. In addition, in this study, triple therapy was not initiated in the patients in the treatment group in the first 24 h following the diagnosis of sepsis or intensive care and triple therapy was given to the patients at a later time as the last step. As stated in the study of Marik et al.,[23] the maximum benefit of triple therapy is likely to be observed within 24 h after the diagnosis of sepsis and the introduction of the ICU.

In conclusion, it is known that ascorbic acid and thiamine levels decrease in sepsis and replacement therapies in septic shock give positive results in pilot studies. Treatment of sepsis and septic shock with corticosteroids has positive effects particularly in patients with renal insufficiency. Ascorbic acid, thiamine and steroids have each been used in practice for decades and show efficacy in a variety of indications. Their use is within the acceptable safety range in studies up to now. Recently used in combination, these agents significantly reduce morbidity and mortality in patients with sepsis and septic shock. The presented studies show that high-dose IV ascorbic acid, thiamine, and steroids are safe and effective in sepsis and septic shock, and their combination are promising. If future studies show benefits similar to the study of Marik et al.,[23] it is wise to use this combination therapy in addition to standard care practices in the treatment of sepsis or septic shock.

Based on these studies, steroid use in addition to standard care practices in the treatment of severe sepsis and septic shock has become an officially recommended treatment in the Surviving Sepsis Campaign Guidelines. In addition to standard care practices such as broad-spectrum antibiotic therapy, fluid resuscitation and vasopressor support and hydrocortisone in the treatment of sepsis and septic shock, there are studies suggesting that vitamin C and thiamine replacements can reduce mortality rates and eliminate the need for vasopressors. Transforming these studies into large-scale, multi-center, and prospective studies is of utmost importance both to reduce the incidence of mortality and to improve the quality of life of surviving patients.

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