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Current Role of High Dose Vitamin C in Sepsis Management: A Concise Review

Vitamin C in Sepsis: A Concise Review

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Abstract

Sepsis and septic shock are common diagnosis for patients requiring Intensive Care Unit admission and associated with high morbidity and mortality. In addition to aggressive fluid resuscitation and antibiotic therapy, several other drugs have been tried as adjuvant therapies to reduce the inflammatory response and improve outcomes. Vitamin C has been shown to have several biological actions, including anti-inflammatory and immunomodulatory effects, which may prove beneficial in sepsis management. Initial trials showed improved patient outcomes when high dose vitamin C was used in combination with thiamine and hydrocortisone. These results, along with relative safety of high-dose (supra-physiological) vitamin C encouraged physicians across the globe to add vitamin C as adjuvant therapy in the management of sepsis. However, subsequent large-scale randomised control trials could not replicate these results leaving the world divided regarding the role of vitamin C in sepsis management. Here, we discuss, the rationale, safety profile and the current clinical evidence for the use of high-dose vitamin C in the management of sepsis and septic shock.

Key Words: Ascorbic acid; Critical care; Infection; Sepsis; Septic shock; Vitamin C

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Core Tip: High-dose vitamin C is increasingly used in varied clinical conditions including, sepsis and septic shock. Even though a few initial studies showed remarkable improvements in outcomes, later studies failed to replicate these effects. Through this article, we wish to review the rationale and current clinical evidence for use of vitamin C in the management of patients with sepsis and septic shock.

INTRODUCTION

Vitamin C, or ascorbic acid, is a water-soluble vitamin that acts as an anti-oxidant and as a co-factor for multiple enzymes. For a long known time, vitamin C deficiency has been associated with the occurrence of Scurvy disease. However, in recent years, vitamin C has been established to have different biochemical effects and has been increasingly used in varied clinical conditions that include severe acute pancreatitis, sepsis and cancer.^[1-3] Being a water-soluble vitamin, vitamin C is generally considered to be safe even in high dosages. Though no clear guidelines or recommendations exist for the administration of vitamin C, it is still being used to manage these diseases, even in critically-ill patients. Mortality, associated with sepsis and septic shock, remains high though the disease, its prognosis and management procedures are well established earlier. Intravenous fluid resuscitation and hemodynamic support, early administration of appropriate antibiotics, source control and organ support form the mainstay of therapy.^[4] Over the years, various therapeutic methods that include activated protein C, ulinastatin and vitamin C have been tested as adjuvant therapies to improve the outcomes.^[2,5,6] However, these therapies failed to achieve any significant and meaningful outcome whereas their role in sepsis management remains ambiguous.^[4] In this background, the aim of the current review is to discuss the scientific rationale behind the usage of High-Dose Vitamin C (HDVC) upon patients with sepsis and septic shock and evaluate its clinical evidence.

RATIONALE

In general, normal serum contains more than 50 $\mu\text{mol/L}$ vitamin C.^[7] However, acutely-ill patients exhibit rapid reduction in their vitamin C levels, while critically-ill patients, especially those with sepsis, show extremely low vitamin C levels (below 11 $\mu\text{mol/L}$), in spite of the recommended enteral and parenteral nutritional intakes.^[8] Moreover, commonly-employed organ-support Intensive Care Unit (ICU) interventions like Continuous Renal Replacement Therapy (CRRT) also reduce the levels of water-soluble vitamins like vitamin C.^[9]

Vitamin C exhibits several biochemical effects that may potentially benefit the management of patients with sepsis and septic shock (Table 1).^[10,11] Sepsis releases

several Reactive Oxygen Species (ROS) which are capable of causing severe injury to lipids, proteins and nucleic acid that in turn results in endothelial and mitochondrial dysfunction, cell death and ultimately Multiple Organ Dysfunction Syndrome (MODS). Vitamin C exerts its anti-oxidant effects by scavenging these ROS. Further, it also helps in recycling other anti-oxidants like vitamin E and tetrahydrobiopterin (BH₄). Thus, it plays a major role in preventing oxidative damage and cell death.^[12,13]

Sepsis tends to reduce the functions of Adenosine Triphosphate (ATP) and causes bioenergetic failure of mitochondria, secondary to oxidative damage caused by mitochondrial ROS and alterations in fatty acid metabolism.^[14] Vitamin C exhibits anti-oxidant effect and prevents the oxidative damage and it also helps in carnitine production that improves fatty acid metabolism in mitochondria.^[15] These actions may be helpful in the prevention of cell death, leading to septic cardiomyopathy and MODS. Sepsis causes microvascular dysfunction which reduces the arteriolar reactivity to vasoconstrictors. This phenomenon results in vasodilation and shock. Vitamin C acts as a co-factor for the enzymes that are required for the synthesis of catecholamines and vasopressors. Thus, it enhances the synthesis of these enzymes and improves arteriolar sensitivity to vasopressors by inhibiting endothelial expression of inducible Nitric Oxide Synthase (iNOS). In addition, vitamin C also has several immuno-modulatory and anti-inflammatory effects that help in abating cytokine storm associated with sepsis-induced MODS.^[10,11,16]

CLINICAL STUDIES

Several Randomised Controlled Trials (RCTs) were conducted in recent years to explore the plausibility of clinical benefits, achieved from the antioxidative effect of vitamin C, in reducing sepsis-induced tissue injury (table 2). The authors conducted a systematic search using keywords such as 'Vitamin C' OR 'Ascorbic acid' AND Sepsis OR "Septic Shock" in PubMed and Google Scholar and found a total of 17 RCTs suitable for the current analysis. Out of the 17, five studies were about the application of vitamin C alone in patients with sepsis.^[17-21] The current study followed a heterogeneous design

with different doses of vitamin C, monotherapy *vs* combination therapy with thiamine and hydrocortisone and the timing of administration.

Isolated Vitamin C Therapy

Out of the RCTs considered, five Randomized Control Trials (RCTs) compared vitamin C with placebo in patients with sepsis. Different doses were used in the studies under consideration.^[17-21] All the studies, except one, failed to infer any clinically meaningful difference with the usage of vitamin C.^[18] CITRIS-ALI trial compared vitamin C (at a dose of 50 mg/kg/6 hly) with a placebo in patients with sepsis and Acute Respiratory Distress Syndrome (ARDS). No significant difference was found in the mean change of Sequential Organ Failure Assessment (SOFA) scores between the groups considered, from baseline to 96 h. The changes in C-reactive protein (CRP) and thrombomodulin levels, at 168 h, were also statistically non-significant. In terms of subgroup analysis, the 28-day mortality rate (without adjustment for multiple comparisons) was found to be significantly lower in vitamin C group (29.8% *vs.* 46.3%; $P = 0.03$).^[17]

The largest and the most recently published LOVIT study was a phase III, multicentre RCT that involved 35 medical-surgical ICUs which spanned across Canada, France, and New Zealand. The study included patients with suspected or proven infection and those who were on vasopressor support. Vitamin C was intravenously administered once for 6 h, at a dosage of 50 mg/kg, up to 96 h to 429 patients in intervention group. On the other hand, Placebo was administered to 434 patients who belonged to control group. The administration of thiamine and glucocorticoids were left to the clinical discretion of the treating physician. The primary outcome i.e., a composite of death or persistent organ dysfunction at 28 days, was significantly higher in intervention (vitamin C) group *vs* control group (44.5% *vs.* 38.5%; risk ratio: 1.21; 95% Confidence Interval, CI 1.04-1.40; $P = 0.01$). However, no significant difference was found with the individual components of composite primary outcome: mortality or persistent organ dysfunction, organ dysfunction free-days at 28 days, SOFA scores at pre-defined time intervals from days 1-28, 6-month survival, and health-related quality of life. The study outcomes not only inferred the lack of benefit but also provided insights on possible

harm caused by high dosage administration of vitamin C in patients with sepsis and septic shock.^[20]

Vitamin C as a part of combination therapy

Marik *et al*, conducted a single-centre retrospective study involving 47 patients. This study compared cocktail therapy that includes Hydrocortisone, Ascorbic acid and Thiamine (HAT) with a control group (only thiamine and ascorbic acid were administered) among patients with severe sepsis and septic shock. The authors recorded a low hospital mortality rate in treatment group (8.5% vs. 40.4%, $P < 0.001$). The dosage regimen was as follows; vitamin C at 1.5 g/hour/6 hly; hydrocortisone at 50 mg/6 hly, and thiamine at 200 mg/12 h. Moreover, the mean duration of the vasopressors, used for shock, was also significantly shorter in intervention arm (18.3 vs. 54.9 h, $P = 0.001$).^[22] This observational study started a debate on the suggested possible benefits of cocktail therapy among patients with septic shock. Subsequently, multiple RCTs were conducted to validate the findings of this study.

The VITAMINS trial, a multicentric RCT involving 211 patients, evaluated the effectiveness of a combination of vitamin C (1.5 g/6 hly), thiamine (200 mg/12 hly), and hydrocortisone (50 mg/6 hly) in patients suffering from septic shock. To conduct primary analysis, 107 patients were recruited for intervention arm and 104 patients under control arm. The eligibility criteria for this study were as follows; a primary diagnosis of septic shock with acute increase in SOFA score by two points or more, a lactate level > 2 mmol/L, and the requirement for vasopressor support for at least 2 h, prior to enrolment. The study found no significant difference between the groups in terms of primary outcome, duration of time alive and vasopressor-free days until day 7 [122.1 (76.3–145.4 h) vs: 124.6 (82.1–147.0 h), $P = 0.83$]. Among the secondary outcomes too, no significant difference was found upon 28 days, 90 days, ICU-, or hospital-mortality between the groups. Further, the two groups also exhibited similar secondary outcomes like vasopressor-free days, mechanical ventilation-free days, and renal replacement-free days. While SOFA scores got reduced by day 3 in both the groups; the

decline was marginally higher in intervention group. In this study, two patients had adverse events (fluid overload and hyperglycemia, one each) in intervention group.^[23]

A multicentre RCT (ACTS trial) was conducted among 205 septic shock patients randomised into placebo ($n = 102$) and intervention arm ($n = 103$) with intravenous Vitamin C (1500 mg/6 hly), hydrocortisone (50 mg/6 hly), and thiamine (100 mg/6 hly) for 4 days. No significant change was observed in SOFA score (difference between baseline and SOFA score at 72 h) between intervention *vs* placebo (-0.8 ; 95%CI, -1.7 to 0.2 ; $P=0.12$). Further, no significant difference was found in the secondary outcomes too such as incidence of Acute Kidney Injury (AKI) and ventilator-free days. Shock-free days were found to be higher in intervention group (median difference of 1 day, 95%CI, 0.2 - 1.8 days; $P < 0.01$).^[24]

In another multicentric RCT (VICTAS trial) conducted among patients with sepsis and septic shock ($n = 252$), a cocktail of vitamin C (1.5 gm/6 hly), thiamine (100 mg/6 hly), and hydrocortisone (50 mg/6 hly) was used, commencing within four hours of randomization for 4 days. On the other hand, a matching placebo was administered in control group ($n = 249$). The trial was prematurely terminated due to lack of funding though the actual plan was to recruit 2000 patients. No significant difference was found in terms of primary outcomes such as ventilator- and vasopressor-free days for the first 30 days [25 days (0-29 days) *vs.* 26 days (0-28 days), $P = 0.85$]. Further, no significant difference was found between day-30 mortality too between the groups (22% *vs* 24%). In addition to these, no serious adverse events were reported during the study. This study, although terminated early, did not reveal any difference with vitamin C cocktail in patients with sepsis, including respiratory or cardiovascular dysfunction.^[25]

Similar findings were reported in another multi-center RCT (ATESS trial) conducted in South Korea. Patients, with septic shock in emergency department, were randomized to receive either vitamin C (50 mg/kg) and thiamine (200 mg/12 hly for 48 h) in the intervention arm ($n = 53$) or placebo ($n = 58$) in control group. Hydrocortisone (200 mg/day) and intravenous vasopressin infusion were administered in both the arms of patients who required high dosage norepinephrine. No statistically significant

difference was found in the primary outcome whereas the SOFA score (difference between the baseline and 72-hours score) got significantly changed between intervention and placebo [3, (- 1 to 5) vs. 3, (0-4), $P = 0.96$]. Further, there was no significant difference between the intervention arm and placebo in baseline vitamin C or thiamine levels. After the treatment, vitamin C and thiamine levels were found to have increased in the intervention group. However, there was no significant difference observed in any of the secondary outcomes; mortality at day-7, -28, or -90, shock reversal, ventilator-free days, incidence of AKI, and reduction of CRP, or procalcitonin.^[26]

Several non-randomized trials have also been conducted earlier to evaluate the role of vitamin C, either as a single entity or as a part of combination therapy, in the management of sepsis (table 3).

Metanalysis of vitamin C in sepsis

Various systematic reviews and meta-analyses have been published on vitamin C in sepsis, with conflicting results on the short-term mortality (table 4). However, no effect was found in the trials with long-term mortality. A recent metanalysis by Agarwal *et al*, with 41 RCTs and 4915 patients (including recently published LOVIT trial), explored the effect of intravenous vitamin C as monotherapy or combination therapy among hospitalized patients with severe infection. With a low-certainty evidence, there was a trend towards reduced in-hospital mortality (21 RCTs, 2762 patients, risk ratio, $RR=0.88$ [95%CI, 0.73-1.06]), 30-day mortality (24 RCTs, 3436 patients, $RR=0.83$ [0.71-0.98]), and early mortality (34 RCTs, 4366 patients, $RR=0.80$ [0.68-0.93]) with vitamin C. However, on sensitivity analysis involving published trials which were blinded and with a low risk of bias, the impact of vitamin C was attenuated with no statistical significance. The RR of hospital mortality (6 RCTs, 1371 patients) was 1.07 (0.92-1.24), moderate certainty evidence; 30-day mortality (9 RCTs, 2057 patients) was 0.88 (0.71-1.10), low certainty evidence; and early mortality (11 RCTs, 2214 patients) was 0.88 (0.73-1.06), with low certainty evidence. With moderate certainty evidence increased 90-day mortality was

suggested in 5 RCTs, including 1722 patients (RR=1.07, 0.94-1.21). The reason for heterogeneity was few trials with large treatment effects because of either being a single centre, or small sample size. The RR of early mortality in trials reporting 90-day mortality was 1.05 (0.91-1.21). Among the adverse events, there were no major adverse events, except an increased risk of hypoglycemia (1 RCT, 862 patients, RR=1.20 [0.69-2.08]), moderate certainty of evidence. The result of other secondary outcomes was mixed with reduction of duration and use of mechanical ventilation and increased risk of AKI or need of RRT, based on low-certainty evidence. ³ No credible subgroup effects were observed related to cointerventions (monotherapy vs. combined therapy), dose of vitamin C, or the type of infection (SARS-CoV-2 vs. others).^[44]

DOSING

Different authors have tried several different dosing regimens. Higher doses of intravenous Vitamin C are also being prescribed regularly, with doses up to 100 g/day used to manage patients with sepsis.^[50] Even “high-dose” ¹ is not clearly defined and is arbitrarily considered a dose of more than 2-10 gm/day in adults, by different authors.^[57,58]

The current literature suggests using six hourly dosage for vitamin C in order to alleviate the deficiency, achieve steady plasma levels rapidly, and maintain normal serum levels. This dosing schedule may also be able to rapidly normalize the neutrophil ascorbic acid levels.^[36,39] Even though intravenous formulations are generally preferred in critically ill patients, especially those in shock, and may rapidly increase the serum vitamin C levels, no difference in clinical efficacy has been reported between intravenous and oral formulations of vitamin C.^[59,60]

ADVERSE EFFECTS

¹ As it is a water-soluble vitamin, vitamin C is generally considered safe, even when used in high doses. Most of the large trials evaluating the efficacy of vitamin C have not assessed adverse effects as a primary objective. Hence, the data regarding adverse events has largely come from case reports, case series and meta-summary of case reports.^[61] ¹ Most commonly reported side effects are mild and include interference with

laboratory tests, lethargy, fatigue, phlebitis, glycemic disturbances (hypo or hyperglycemia), hypernatremia, muscle cramps, nausea, vomiting, headache, altered mental status, syncope, methemoglobinemia, oxalosis and renal stones. However, rarely patients may develop life-threatening complications like haemolysis, AKI and disseminated intravascular coagulation.^[62,63] The probability of developing complications is reported to be higher in patients with glucose-6-phosphate dehydrogenase (G6PD) deficiency and those with underlying renal dysfunction.^[61] Even though vitamin C has anti-oxidant properties, when used in higher doses, may deplete the intra-erythrocyte glutathione stores and cause oxidative stress. Patients with G6PD deficiency are unable to replenish these glutathione stores and develop haemolysis secondary to oxidative damage.^[64,65]

DISCUSSION

Despite a pathophysiological rationale, the evidence does not support the use of vitamin C in sepsis. Indeed, there was a trend towards harm from the primary outcome in the LOVIT trial. However, the primary outcome was composite, and its components did not reach statistical significance. The harm was not seen with other RCTs. In the LOVIT trial, the intervention arm had more patients in shock and on invasive mechanical ventilation at the baseline compared to the control arm. This imbalance in baseline characteristics between the groups may explain the higher incidence of organ dysfunction. Furthermore, despite excluding patients staying >24 h in ICU, the time gap between the actual onset of sepsis and administration of vitamin C is unclear.^[20]

We know sepsis is a syndrome and has proven to be a graveyard of various therapies modulating inflammation. The role of vitamin C, if there is, may be in the initial phase of hyperinflammation or cytokine storm and release of reactive oxygen species. Besides, the heterogenous cohort used in these RCTs failed to consider the sepsis phenotypes based on the level of inflammation. Finally, baseline vitamin C levels were not measured in all the trials, and a fixed dose therapy without measuring therapeutic levels may have caused inconsistent results.

In the absence of current evidence showing any clinical benefits, the recent surviving sepsis guidelines suggests against using vitamin C for managing patients with sepsis and septic shock.^[4] The clinical practice at our institute is also in accordance to these latest recommendations and we refrain from making vitamin C a part of our routine sepsis management regimen. The future may be the individualization of these therapies using different disease models based on the aetiology of sepsis, illness severity, and degree of inflammation.

FURTHER TRIALS

Presently, there are more than 30 ongoing clinical trials to evaluate the effect of vitamin C in the management of sepsis and septic shock, in different parts of the world. These trials are evaluating the role of different doses (up to 12 g/day), different patient populations (alcoholic hepatitis, acute lung injury, patients on invasive mechanical ventilation) and different combinations (along with steroids, thiamine, pyridoxine, cyanocobalamine). Many of these are randomized multi-center trials (CEMVIS, REVISTA-DOSE, c-easie) which may shed light on many of the unanswered questions regarding the utility of vitamin C in sepsis management. Ongoing studies in different cohorts like patients with COVID-19 (LOVIT-COVID, REMAP-CAP), burn (VICTORY), post-cardiac arrest (VITaCCA) and/or cardiac surgery patients (advanceCSX) may answer the question of whether vitamin C can produce clinically meaningful outcomes in more specific patient cohorts.

CONCLUSION

Theoretically, vitamin C has been established to protect cells from oxidative damage, reduce inflammatory response, maintain immune functions and increase the hemodynamic reserve. All these biological actions may be beneficial in the management of sepsis and septic shock. However, in the aftermath of recent interests and several multi-center trials, it can be concluded that there is still a lack of strong evidence to

prove its clinical benefits. Contrary to popular belief, use of intravenous HDVC may rarely be associated with adverse effects like haemolysis, especially in vulnerable patients like those with G6PD deficiency or underlying renal dysfunction. Hence, routine use of HDVC is presently not recommended in the management of sepsis or septic shock.

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