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Current role of high dose vitamin C in sepsis management: A concise review

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Abstract

Sepsis and septic shock are common diagnoses 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 an 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.

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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 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 at high dosages. Although 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 and 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) in 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 a 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 results in the release of 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].

Table 1 Biological effects of vitamin C

Biological effects of vitamin C	Mechanisms of action
Antioxidant properties	Reduced production of reactive oxygen species; Reduced production of endothelial nitric oxide
Prevention of mitochondrial dysfunction	Reduction of oxidation injury; Reduces apoptosis
Prevention of septic cardiomyopathy	Reduction of oxidation injury; Increased carnitine synthesis; Reduces apoptosis
Prevention of micro and macro vascular dysfunction	Acts as a co-factor for synthesis of catecholamines (epinephrine, norepinephrine) and vasopressin; Inhibition of iNOS expression
Anti-inflammatory effects	Suppresses activation of nuclear factor kappa-B (NF- κ B); Inhibits tumor necrosis factor- α ; Reduces pro-inflammatory cytokines like high mobility group box-1; Lowers histamine levels
Immune enhancing effects	T-cell maturation and modulation; Improves neutrophil chemotaxis and phagocytosis; Enhances oxidative killing; Promotes proliferation of lymphocytes; Stimulates interferon production; Increased antibody production

CLINICAL STUDIES

Several randomised controlled trials (RCTs) have been 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 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 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]. The CITRIS-ALI trial compared vitamin C (at a dose of 50 mg/kg q6h) with a placebo in patients with sepsis and acute respiratory distress syndrome. 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-d mortality rate (without adjustment for multiple comparisons) was found to be significantly lower in the 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 the intervention group. On the other hand, a placebo was administered to 434 patients who belonged to the control group. The administration of thiamine and glucocorticoids was left to the clinical discretion of the treating physician. The primary outcome, *i.e.*, a composite of death or persistent organ dysfunction at 28 d, was significantly higher in the intervention (vitamin C) group *vs* the 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 in the individual components of composite primary outcome: Mortality or persistent organ dysfunction, organ dysfunction-free days at 28 d, SOFA scores at pre-defined time intervals from days 1-8, 6-mo 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*[22] conducted a single-centre retrospective study involving 47 patients. This study compared cocktail therapy that included hydrocortisone, ascorbic acid, and thiamine (HAT) with a control group (standard care) among patients with severe sepsis and septic shock. The authors recorded a low hospital mortality rate in the treatment group (8.5% *vs* 40.4%, $P < 0.001$). The dosage regimen was as follows: Vitamin C at 1.5 g/h q6h, hydrocortisone at 50 mg q6h, and thiamine at 200 mg/12 h. Moreover, the mean duration of the vasopressors, used for shock, was also significantly shorter in the intervention arm (18.3 h *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.

Table 2 Randomized Trials of vitamin C in sepsis

No.	Title	Ref.	Acronym	Country of origin	Study design	Sample size in control arm	Sample size in intervention arm	Intervention summary	Results in brief
Studies using isolated vitamin C									
1	Intravenous Vitamin C in Adults with Sepsis in the Intensive Care Unit	Lamontagne <i>et al</i> [20], 2022	LOVIT Trial	Canada	RCT	437	435	Intravenous vitamin C (at a dose of 50 mg/kg body weight) 6 hourly for 96 h	This trial reported significantly higher composite primary outcome (risk of mortality OR persistent organ dysfunction at 28 d) in vitamin C group. One patient had a severe hypoglycemic episode and another had a serious anaphylaxis event.
2	Intravenous vitamin C administration to patients with septic shock: a pilot randomised controlled trial	Rosengrave <i>et al</i> [19], 2022		New Zealand	RCT	20	20	Intravenous vitamin C (at a dose of 25 mg/kg of body weight every 6 h) for up to 96 h, or until death or discharge	Treatment with intravenous vitamin C did not result in reduction of mean dose and duration of vasopressor infusion. Both the groups were comparable for rise in inflammatory markers, length of ICU stay, length of hospital stay, and mortality.
3	Early use of high-dose vitamin C is beneficial in treatment of sepsis	Lv <i>et al</i> [18], 2020		China	RCT	56	61	Intravenous vitamin C 3.0 g in 5% dextrose (100 ml/time, 2 times/d)	Treatment with vitamin C resulted in a significant reduction in the 28-d mortality. There was a significant reduction in SOFA score at 72 h and duration of vasopressor use, also there was increased clearance of procalcitonin.
4	Effect of Vitamin C Infusion on Organ Failure and Biomarkers of Inflammation and Vascular Injury in Patients With Sepsis and Severe Acute Respiratory Failure: The CITRIS-ALI Randomized Clinical Trial	Fowler <i>et al</i> [17], 2019	CITRIS-ALI RCT	United States	RCT	83	84	Intravenous infusion of vitamin C (50 mg/kg in dextrose 5% in water, <i>n</i> = 84) every 6 h for 96 h	There was no significant difference in SOFA score at 96 h, and levels of marker of inflammation (CRP) and vascular injury (thrombomodulin) at 168 h.
5	Effect of vitamin C administration on neutrophil apoptosis in septic patients after abdominal surgery	Ferrón-Celma <i>et al</i> [21], 2008		Spain	PD interventions RCT study	10	10	The vitamin C group received 450 mg/d of the vitamin in 3 doses	Vitamin C treatment in postoperative septic abdominal surgery patients have an antiapoptotic effect on peripheral blood neutrophils, reducing caspase-3 and PARP levels, and increasing BCL-2 levels. However this effect is not maintained all the time.
Studies using vitamin C in combination therapy									
6	Effect of Supplementation of Vitamin C and Thiamine on the Outcome in Sepsis: South East Asian Region	Ap <i>et al</i> [27], 2022		India	RCT	20	20 + 20 + 20	Intervention group received vitamin C, thiamine, both, and neither, respectively. Vitamin C (2 g 8 hourly) and thiamine (200 mg 12 hourly) were given intravenously for 5 d	Intervention with vitamin C and thiamine did not reduce mortality. The vitamin C level and thiamine level were significantly lower than those in healthy controls.
7	Biomarker Analysis for Combination Therapy of Vitamin C and Thiamine	Park <i>et al</i> [34], 2022	Post hoc ATESS	South Korea	RCT (post hoc analysis)	52	45	Intravenous vitamin C (50 mg/kg, maximum single dose 3 g) and thiamine	Baseline biomarker levels (IL-6, IL-10, AP2, and S100β) at 72 h were not significantly different

	in Septic Shock: A Post-Hoc Study of the ATESS Trial							(200 mg) administration every 12 h for a total of 48 h	between the treatment and the placebo groups, also the rate of reduction was not significantly different between the two groups.
8	Effect of Vitamin C, Thiamine, and Hydrocortisone on Ventilator- and Vasopressor-Free Days in Patients With Sepsis: The VICTAS Randomized Clinical Trial	Sevransky JE <i>et al</i> [25], 2021	VICTAS Trial	United States	RCT	252	249	Vitamin C (1.5 G), thiamine (100 mg), and hydrocortisone (50 mg) every 6 h	In patients with sepsis and septic shock, treatment with combination therapy did not reduce ventilator days and vasopressor use. Mortality at 30 d was also comparable between the groups.
9	Vitamin C Therapy for Routine Care in Septic Shock (ViCTOR) Trial: Effect of Intravenous Vitamin C, Thiamine, and Hydrocortisone Administration on Inpatient Mortality among Patients with Septic Shock	Mohamed <i>et al</i> [33], 2020	ViCTOR Trial	India	RCT	43	45	Intravenous combination of vitamin C (1.5 g every 6 h), thiamine (200 mg every 12 h), and hydrocortisone (50 mg every 6 h) within 6 h of onset of septic shock admission	This trial found no difference in all-cause mortality in the two groups. The data reported earlier reversal of septic shock but no difference in improvement of SOFA score at 72 h, use of vasoactive substances, or use of mechanical ventilation.
10	Combined Treatment with Hydrocortisone, Vitamin C, and Thiamine for Sepsis and Septic Shock: A Randomized Controlled Trial	Chang <i>et al</i> [32], 2020	HYVCTSSS	China	RCT	40	40	Combination therapy with hydrocortisone (50 mg every 6 h for 7 d), vitamin C (1.5 g every 6 h for 4 d), and thiamine (200 mg every 12 h for 4 d)	Combination therapy did not reduce 28 d all-cause mortality in sepsis and septic shock patients. However, it was associated with 72-h change in Sequential Organ Failure Assessment score improvement. The treatment group exhibited more incidents of hypernatremia.
11	Usefulness of Antioxidants as Adjuvant Therapy for Septic Shock: A Randomized Clinical Trial	Aisa-Alvarez <i>et al</i> [28], 2020		Mexico	RCT	18	18 + 18 + 18 + 18	Enterally administered tablets of NAC 600 mg every 12 hourly. Further, 50 mg of MT in capsules of 5 mg were given to patients once a day, and 1 mg vitamin C tablets were administered every 6 h. Vitamin E capsules of 400 units were given every 8 h for 5 d	Antioxidant therapy helps to regulate inflammation in septic patients with shock. Vitamin C therapy in pulmonary sepsis increases vitamin C serum levels and decreases levels of inflammatory marker like CRP, PCT, and NO ³⁺ /NO ²⁻ .
12	Effect of Ascorbic Acid, Corticosteroids, and Thiamine on Organ Injury in Septic Shock: The ACTS Randomized Clinical Trial	Moskowitz <i>et al</i> [24], 2020	ACTS RCT	United States	RCT	102	103	Parenteral vitamin C (1500 mg), hydrocortisone (50 mg), and thiamine (100 mg) every 6 h for 4 d	Combination therapy with ascorbic acid, corticosteroids, and thiamine did not lead to a significant reduction of SOFA score in septic shock patients during the first 72 h after enrolment. Data from this trial do not support routine use of combination therapy in septic shock.
13	Combination therapy of vitamin C and thiamine for septic shock: a multi-centre, double-blinded randomized, controlled study	Hwang <i>et al</i> [26], 2020	ATESS Trial	South Korea	RCT	58	53	Vitamin C (50 mg/kg, maximum single dose 3 g) and thiamine (200 mg) administration every 12 h for a total of 48 h intravenously	Vitamin C therapy and thiamine administration did not improve organ function and need for organ support despite improvement in levels of these vitamins in early phase of septic shock.
14	Outcomes of Metabolic Resuscitation Using Ascorbic Acid, Thiamine, and Glucocorticoids in the Early Treatment of Sepsis: The ORANGES Trial	Iglesias <i>et al</i> [29], 2020	ORANGES trial	United States	RCT	69	68	Ascorbic acid 1500 mg q6h, thiamine 200 mg every 12 h, and hydrocortisone 50 mg q6h for a maximum of 4 d	Combination therapy resulted in quicker reversal of shock; however, no difference was found in reversal of organ dysfunction or other secondary outcomes.
15	Effect of Vitamin C, Hydrocortisone, and Thiamine vs Hydrocortisone Alone on Time Alive and Free of Vasopressor Support Among Patients	Fujii <i>et al</i> [23], 2020	VITMAINS RCT	Japan	RCT	107	109	Intravenous vitamin C (1.5 g every 6 h), hydrocortisone (50 mg every 6 h), and thiamine (200 mg every 12 h), given in intervention group and intravenous	Findings from this trial suggest that combination therapy does not lead to rapid resolution of septic shock in comparison to hydrocortisone alone with no significant improvement in overall mortality

With Septic Shock: The VITAMINS Randomized Clinical Trial							hydrocortisone (50 mg every 6 h) alone in comparison group until shock resolution or up to 10 d	with intervention. No serious adverse events were reported.
16	Combination of vitamin C, thiamine and hydrocortisone added to standard treatment in the management of sepsis: results from an open label randomised controlled clinical trial and a review of the literature	Wani <i>et al</i> [30], 2020	India	RCT	50	50	Combination of vitamin C (1.5 g q6h for 4 d), thiamine (200 mg q12h for 4 d), and hydrocortisone (50 mg q6h for 7 d/ICU discharge, taper over 3 d)	Combination therapy does not improve in hospital mortality and mortality at 30 d. However, lactate clearance was faster and vasopressor use was lower in intervention group.
17	The effects of intravenous antioxidants in patients with septic shock	Galley HF <i>al</i> [31], 1997	United Kindom	RCT	14	16	Antioxidants (n-acetylcysteine 150 mg/kg for 30 min then 20 mg/kg/h plus bolus doses of 1 g ascorbic acid and 400 mg α -tocopherol)	Basal vitamin C was low and redox-reactive iron was elevated in all patients. Levels of vitamin C were increased but overall antioxidant capacity was unaffected after supplementation. Heart rate cardiac index increased and systemic vascular resistance index decreased in patients treated with antioxidants.

AP2: Angiopoietin-2; CRP: C-reactive Protein; DOI: Digital object identifier; ICU: Intensive care unit; IL-10: Interleukin-10; IL-6: Interleukin-6; MT: Melatonin; NAC: N-acetyl cysteine; NO2: Nitrite; NO3: Nitrate; PARP: Poly (ADP-ribose) polymerase; PCT: Procalcitonin; PMID: PubMed unique identifier; S100 β : S100 calcium-binding protein B; SOFA: Sequential organ failure assessment score.

The VITAMINS trial, a multicentric RCT involving 211 patients, evaluated the effectiveness of a combination of vitamin C (1.5 g q6h), thiamine (200 mg q12h), and hydrocortisone (50 mg q6h) in patients suffering from septic shock. To conduct primary analysis, 107 patients were recruited for the intervention arm and 104 patients under the control arm. The eligibility criteria for this study were as follows: A primary diagnosis of septic shock with an 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 in 28 d, 90 d, 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 the intervention group. In this study, two patients had adverse events (fluid overload and hyperglycemia, one each) in the intervention group[23].

A multicentre RCT (ACTS trial) was conducted among 205 septic shock patients randomised into either a placebo ($n = 102$) or an intervention arm ($n = 103$) with intravenous vitamin C (1500 mg q6h), hydrocortisone (50 mg q6h), and thiamine (100 mg q6h) for 4 d. 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 the intervention group (median difference of 1 d; 95%CI: 0.2-1.8 d; $P < 0.01$)[24].

In another multicentric RCT (VICTAS trial) conducted among patients with sepsis and septic shock ($n = 252$), a cocktail of vitamin C (1.5 g q6h), thiamine (100 mg q6h), and hydrocortisone (50 mg q6h) was used, commencing within 4 h of randomization for 4 d. On the other hand, a matching placebo was

administered in the control group ($n = 249$). The trial was prematurely terminated due to the 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 d [25 d (0-29 d) *vs* 26 d (0-28 d), $P = 0.85$]. Further, no significant difference was found between 30-d mortality 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 q6h for 48 h) in the intervention arm ($n = 53$) or placebo ($n = 58$) in the control group. Hydrocortisone (200 mg/d) 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-h score) significantly changed between the intervention and placebo groups [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, including 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).

Meta-analysis 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 metaanalysis by Agarwal *et al*[44], 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 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-d 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), with moderate certainty evidence; that of 30-day mortality (9 RCTs, 2057 patients) was 0.88 (0.71-1.10), with low certainty evidence; and that of early mortality (11 RCTs, 2214 patients) was 0.88 (0.73-1.06), with low certainty evidence. With moderate certainty evidence, increased 90-d mortality was suggested in five RCTs, including 1722 patients (RR = 1.07, 0.94-1.21). The reason for heterogeneity was that few trials with large treatment effects were either single centre, or had small sample size. The RR of early mortality in trials reporting 90-d 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]), with 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. 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/d used to manage patients with sepsis[50]. Even “high-dose” is not clearly defined and is arbitrarily considered a dose of more than 2-10 g/d 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

As a water-soluble vitamin, vitamin C is generally considered safe, even when used at high doses. Most

Table 3 Non randomized studies of vitamin C in sepsis

No.	Title	Ref.	Country of origin	Study design	Sample size in control arm	Sample size in intervention arm	Intervention summary	Results in brief
Studies using isolated vitamin C								
1	High dose intravenous vitamin C treatment in Sepsis: associations with acute kidney injury and mortality	McCune <i>et al</i> [35], 2021	United States	Cohort study (retrospective cohort)	1178	212	Cohort of patients who have received at least one dose of 1.5 g IV vitamin C	Vitamin C therapy was associated with significant chances of AKI and death.
2	Effect of high-dose intravenous vitamin C on point-of-care blood glucose level in septic patients: a retrospective, single-center, observational case series	He <i>et al</i> [38], 2020	China	Observational case series		82	Patients with septic shock on admission received 100 mg/kg/d, while other patients received < 100 mg/kg/d	High-dose vitamin C therapy may interfere with point-of-care glucose testing results.
3	Pharmacokinetic data support 6-hourly dosing of intravenous vitamin C to critically ill patients with septic shock	Hudson EP <i>et al</i> [36], 2019	Australia	Observational PK study		11	Patients received 1.5 g intravenous vitamin C every 6 h	Injectable vitamin C 1.5 g every 6 h helps in correction of vitamin C deficiency and hypovitaminosis C, and it also provides appropriate dosing schedule for vitamin C supplementation in septic shock.
4	Accuracy of Point-of-Care Blood Glucose Level Measurements in Critically Ill Patients with Sepsis Receiving High-Dose Intravenous Vitamin C	Smith <i>et al</i> [37], 2018	United States	Observational PK study		5	Patients who have received vitamin C 1500 mg intravenously two or more doses and had point of care blood glucose checked and laboratory venous BG levels measured within 1 h of each other during vitamin C therapy	The accuracy and agreement of POC BG did not have significant interference during vitamin C treatment in sepsis.
5	Phase I safety trial of intravenous ascorbic acid in patients with severe sepsis	Fowler <i>et al</i> [39], 2014	United States	Phase I safety trial		24 total in 1:1:1 ratio	Patients with severe sepsis in the medical intensive care unit were randomized 1:1:1 to receive intravenous infusions every 6 h for 4 d of ascorbic acid: Lo-AscA (50 mg/kg/24 h, <i>n</i> = 8), or Hi-AscA (200 mg/kg/24 h, <i>n</i> = 8), or placebo (5% dextrose/water, <i>n</i> = 8)	Intravenous vitamin C infusion is safe and tolerated well and may have a positive impact on endothelial injury, the extent of multiple organ failure, and levels of inflammatory biomarkers.
Studies using combination therapies including vitamin C								
6	Adding vitamin C to hydrocortisone lacks benefit in septic shock: a historical cohort study	Chang <i>et al</i> [40], 2020	Canada	Cohort study (retrospective cohort)	88	52	Retrospective cohorts of vitamin C with hydrocortisone and hydrocortisone therapies for 72 h were compared in patients with sepsis or septic shock	Outcomes for hospital mortality, ICU mortality, ventilator free days, vasopressor free days, dialysis use, and duration of ICU admission were comparable between the groups.
7	Hydrocortisone, Vitamin C, and Thiamine for the Treatment of Severe Sepsis and Septic Shock: A Retrospective Before-After Study	Marik <i>et al</i> [22], 2017	United States	Cohort study (before and after study)	47	47	Intravenous vitamin C (1.5 g q6h for 4 d or until ICU discharge), hydrocortisone (50 mg q6h for 7 d or until ICU discharge followed by a taper over 3 d) as well as intravenous thiamine (200 mg q12h for 4 d or until ICU discharge)	Results of this study suggest that the early use of intravenous vitamin C, together with corticosteroids and thiamine, prevents progressive organ dysfunction, including acute kidney injury, and reduces the mortality of patients with severe sepsis and septic shock.
Other studies								

9	Plasma Cortisol, Aldosterone, and Ascorbic Acid Concentrations in Patients with Septic Shock Do Not Predict Treatment Effect of Hydrocortisone on Mortality. A Nested Cohort Study	Cohen <i>et al</i> [42], 2020	Australia and NZ	Cohort Study (nested cohort study)			Levels of total and free plasma cortisol and aldosterone were measured along with quantitatively measured vitamin C levels	In patients with septic shock, plasma aldosterone and ascorbic acid concentrations are not associated with outcome.
10	Vitamin C levels amongst initial survivors of out of hospital cardiac arrest	Gardner <i>et al</i> [43], 2020	United States	Observational study	34	25 post arrest, 25 post sepsis	Observational	Vitamin C levels are lower in cardiac arrest patients in comparison to healthy patients.
11	Hypovitaminosis C and vitamin C deficiency in critically ill patients despite recommended enteral and parenteral intakes	Carr <i>et al</i> [8], 2017	New Zealand	Observational study	20	24	Patients with septic shock and non-septic aetiology	Critically sick patients have low levels of vitamin C, and septic shock patients have significantly depleted levels.
12	Colistin-associated Acute Kidney Injury in Severely Ill Patients: A Step Toward a Better Renal Care? A Prospective Cohort Study	Dalfino <i>et al</i> [41], 2015	Italy	Cohort (prospective cohort)	39 non AKI	31 AKI	Intervention cohort patients have received colistin at a median daily dose of 9 million IU	Independent renal-protective role emerged for ascorbic acid among other factors responsible for higher chances of AKI.

AKI: Acute kidney injury; Hi-AscA: High dose ascorbic acid; ICU: Intensive care unit; Lo-AscA: Low dose ascorbic acid; POC BG: Point of care blood glucose.

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]. 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 in those with underlying renal dysfunction[61]. Even though vitamin C has anti-oxidant properties, when used at higher doses, it 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 current clinical evidence does not support the use of vitamin C in sepsis. Indeed, there was a trend towards harm observed in the LOVIT trial. However, the primary outcome was composite, and its components did not reach statistical significance. The harm was not seen in 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].

Table 4 Meta-analyses of trials on vitamin C in sepsis

No.	Title	Ref.	Country of origin	Study design	Included studies	Included sample size	Intervention summary	Results in brief
Studies with isolated vitamin C therapy								
1	IV Vitamin C in Critically Ill Patients: A Systematic Review and Meta-Analysis	Patel <i>et al</i> [45], 2022	United States	Meta-analysis	15 RCTs	2490 participants	Compared intravenous vitamin C at high and low doses with placebo among pooled study participants	Intravenous vitamin C therapy is associated with a trend toward reduced overall mortality. Data further reveals that High-dose IV vitamin C was associated with a significant reduction in overall mortality. None of the included trials reported an increase in adverse events related to IV vitamin C therapy.
2	Efficacy of intravenous vitamin C intervention for septic patients: A systematic review and meta-analysis based on randomized controlled trials	Li <i>et al</i> [47], 2021	China	Meta-analysis of RCTs	10 RCTs	1400 patients	Studies that have intravenous vitamin C supplementation were included	Data from this meta-analysis reports improved SOFA score within 72 h but no significant improvement in short term (28-30 d) mortality, long term mortality (90 d), hospital stay, ventilator-free days, ICU-stay in sepsis or septic shock patients.
3	Effect of vitamin C in critically ill patients with sepsis and septic shock: A meta-analysis	Feng <i>et al</i> [48], 2021	China	Meta-analysis of RCTs	9 RCTs	584 patients	Studies with vitamin C treatment in critically sick sepsis and septic shock patients were included	Data from this study finds significant differences in 28-d mortality and dose of vasopressors. However, the ICU length of stay was the same between the two groups.
4	Efficacy of vitamin C in patients with sepsis: An updated meta-analysis	Wei <i>et al</i> [46], 2020	China	Meta-analysis	6 RCTs and 6 observational studies	1176 in control group	This analysis included data from RCTs and observational studies that evaluated the effect of vitamin C in patients with sepsis	This study reports no significant improvement in 28-d or in-hospital mortality. There was also no difference in vasopressor duration and ICU or hospital stay.
Vitamin C as a combination therapy								
5	Thiamine, Ascorbic Acid, and Hydrocortisone As a Metabolic Resuscitation Cocktail in Sepsis: A Meta-Analysis of Randomized Controlled Trials With Trial Sequential Analysis	Assouline B <i>et al</i> [49], 2021	Switzerland	Meta-analysis	8 RCTs	1335 patients	Combination of thiamine, ascorbic acid, and hydrocortisone compared to in patients with sepsis or septic shock	Data in this study was homogenous and intervention led to improved change in SOFA score at 72 h; however, there was no difference in ICU mortality and renal composite outcome (incidence of AKI 3 or need for Renal replacement therapy).
6	The Efficacy of vitamin C, thiamine, and corticosteroid therapy in adult sepsis patients: a systematic review and meta-analysis	Somagutta <i>et al</i> [50], 2021	United States	Meta-analysis	15 studies (8 RCTs and 7 cohort studies)	67349 patients	Combination of HAT treatment in patients with sepsis	Meta-analysis from RCTs concluded that hospital mortality, ICU stay, hospital stay, and renal replacement therapy was not significant. Results from cohort studies have also concluded that hospital mortality, ICU mortality, ICU length of stay, length of hospital stay, change in SOFA score, the use of renal replacement therapy, or vasopressor duration was not significant.
7	Vitamin C, Thiamine, and Hydrocortisone in the Treatment of Sepsis: A Meta-Analysis and Trial Sequential Analysis of Randomized Controlled Trials	Zayed <i>et al</i> [51], 2021	United States	Meta-analysis	6 RCTs	839 patients	Vitamin C, thiamine, and steroid in combination for sepsis and septic shock	Data from this study concluded that there is no significant difference in long term mortality, ICU mortality, incidence of acute kidney injury, hospital length of stay, ICU length of stay, and ICU free days on day 28 between the intervention and control groups. However, there was a significant reduction in SOFA score on 3 rd day.

8	Mortality in septic patients treated with vitamin C: a systematic meta-analysis	Scholz <i>et al</i> [52], 2021	Germany	Meta-analysis	17 studies (randomized and non-randomized, blinded and unblinded, prospective and retrospective, and single- and multi-centre studies)	3133 patients	Vitamin C 1.5 g every 6 h, 100 mg thiamine every 6 h, and 50 mg hydrocortisone every 6 h. However, initiation and duration of the intervention differed considerably within the studies	Pooled analysis in this study indicated no mortality benefit; however, a subgroup analyses revealed an improved survival, if vitamin C treatment was applied for 3-4 d.
9	Effect of adjunctive vitamin C, glucocorticoids, and vitamin B1 on longer-term mortality in adults with sepsis or septic shock: a systematic review and a component network meta-analysis	Fujii <i>et al</i> [53], 2021	Japan	Meta-analysis (network meta-analysis)	43 RCTs	10257 patients	Compared networked interventions of very high dose vitamin C, high dose vitamin C, vitamin C, vitamin B1, and glucocorticoids	This study found that metabolic resuscitation with vitamin C, glucocorticoids, vitamin B1, or combinations of these drugs have no difference in long term mortality. Also they did not find effect of vitamin C or B1 on organ dysfunction or ICU length of stay. However, adding glucocorticoid to the combination therapies reduces the duration of vasopressor therapy and ICU stay.
10	Steroid, ascorbic acid, and thiamine in adults with sepsis and septic shock: a systematic review and component network meta-analysis	Fong <i>et al</i> [54], 2021	Hong Kong	Meta-analysis (component network meta-analysis)	33 RCTs	9898 patients	Additive network meta -analysis was performed, adding vitamin C, glucose corticoid, and thiamine sequentially	Data from this study reveals that combination of glucocorticoid and fludrocortisone improved short-term and longer-term mortality in sepsis and septic shock patients. Steroids shortened the time to resolution of shock and duration of mechanical ventilation. However, there was no evidence to support use of thiamine and vitamin C in sepsis and septic shock.
11	Effect of Combined Hydrocortisone, Ascorbic Acid and Thiamine for Patients with Sepsis and Septic Shock: A Systematic Review and Meta-Analysis	Wu <i>et al</i> [55], 2021	China	Meta-analysis of RCT and observational studies	6 RCTs and 7 observational studies	1559 participants.	This study compared hydrocortisone, thiamine, and ascorbic acid use to usual care or hydrocortisone	Combination therapy associated with significant reductions in duration of vasopressor in RCTs, but not in observational studies. It was associated with lower SOFA score at 72 h both in RCTs and observational studies. Combination therapy associated with lower hospital mortality and higher PCT clearance in observational studies.
12	Thiamine combined with vitamin C in sepsis or septic shock: a systematic review and meta-analysis	Ge <i>et al</i> [56], 2021	China	Systematic review and meta-analysis	7 RCTs	868 patients	Thiamine combined with vitamin C in patients with sepsis or septic shock	Data from this study found no significant differences for in hospital mortality, but have shorter duration of vasopressor use and reduced SOFA score during 72 h.

HAT: Hydrocortisone; ascorbic acid and thiamine combination; ICU: Intensive care unit; IV: Intravenous; RCT: Randomized control trial; SOFA: Sequential organ failure assessment score.

We know that 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 associated with release of ROS. Besides, these RCTs used the heterogeneous cohort and 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 suggest 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/d), different patient populations (alcoholic hepatitis, acute lung injury, and patients on invasive mechanical ventilation), and different combinations (along with steroids, thiamine, pyridoxine, or cyanocobalamin). Many of these are randomized multi-center trials (CEMVIS, REVISTA-DOSE, and 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 and 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 populations.

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.

FOOTNOTES

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