Safety of vitamin C in sepsis: a neglected topic

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Purpose of review
Although vitamin C is essentially a nontoxic vitamin; however, it is important to be aware regarding the safety of high doses before the wide clinical use.

Recent findings
Minor side effects of vitamin C have been reported, many being reported in earlier studies. High doses of vitamin C (up to 1.5 g/kg three times a week as intravenously) were safe in cancer patients with normal renal function and perfect glucose-6-phosphate dehydrogenase activity. As the dose and duration of administration of vitamin C in sepsis are lower and shorter than those used in cancer patients, it seems that it is relatively safe for this population. In ongoing trials, safety of high doses of vitamin C is considered.

Summary
Data regarding the safety of high doses of vitamin C are scant. Until more data become available, caution should be applied in the use of high doses of vitamin C in patients with hemochromatosis, glucose-6-phosphate dehydrogenase deficiency, renal dysfunction, kidney stone, oxaluria, and pediatrics.

Keywords
safety, sepsis, vitamin C

INTRODUCTION

Nowadays role of vitamin C in the management of sepsis is evolving. Most of the known biological functions of vitamin C are related to its antioxidant properties. It blocks reactive oxygen species (ROS) which formed under different stress situations such as sepsis and can damage cellular proteins, lipids, DNA, and impairs mitochondrial function [1,2]. Vitamin C prevents neutrophil-induced lipid oxidation [3] and potentiates functions of other circulatory antioxidants such as alpha-tocopherol and tetrahydrobiopterin [4]. It also is a cofactor for many enzymatic reactions involved in carnitine synthesis, production of catecholamines, vasopressin, cortisol, and works as a stress hormone in sepsis [5,6]. By inhibiting the activation of nuclear factor kappa B that is responsible for proinflammatory cytokines production, vitamin C modulates the immune system responses. It enhances phagocytic activity of leucocytes and reduces superoxide production in macrophages [7]. Vitamin C also inhibits bacterial growth [8].

ROS play a major role in defense against sepsis. Increased endothelial damage and permeability, hypotension, mitochondrial impairment are important elements of multiorgan failure and mortality in septic patients [9]. Inflammatory features, immune paralysis, and oxidative stress are the main targets in the management of sepsis [10].

It has been known for decades that any acute illness could result in a drop in plasma and cellular levels of vitamin C possibly due to decreased intake and absorption, increased metabolism and even redistribution [11,12]. Although nowadays scurvy is a very rare complication, approximately 40% of ICU patients with septic shock have vitamin C serum levels less than 11.3 μmol/l (fasting ascorbate plasma levels more than 34 μmol/l indicate adequate status). Septic patients without shock are likely to have hypovitaminosis C with the serum concentrations less than 23 μmol/l [13] Ascorbic acid plasma levels were in deficient range in 90% of patients with severe sepsis [14]. The lowest vitamin C plasma levels were reported in septic patients

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KEY POINTS

- Nowadays, high doses of vitamin C are used in some centers as an adjunct therapy in severe sepsis and septic shock. It may improve outcome of sepsis.
- Most trials considered effectiveness but not safety of vitamin C as a main endpoint in sepsis. However, no serious concern regarding high doses of vitamin C has been reported in these trials.
- Safety of high doses of vitamin C was considered as a main outcome only in selected patients with cancer. Comparing applied doses and durations of vitamin C in sepsis and cancer, it seems to be a safe intervention in septic patients.
- Electrolytes, acid–base status, renal function, urine analysis, and cell blood count should be monitored during administration of high doses of vitamin C.
- Adequate hydration before, during and after administration of high doses of vitamin C is critical. Also appropriate dilution and rate of administration are important issues.

with multiorgan failure [15▪]. As measurement of vitamin C in serum is not easily available and the deficiency mimics the acute illness symptoms, this usually goes unnoticed. Acute deficiency of vitamin C may contribute to hypotension, inflammatory responses, capillary leakage, microcirculatory dysfunction, impaired immunity and organ failure [16▪]. Low serum vitamin C levels in critically ill patients were associated with increased vasopressor requirements, kidney injury, multiorgan dysfunction and increased mortality [1].

Vitamin C supplementation might have beneficial effects on sepsis outcome. In a recent meta-analysis, it has been that vitamin C improved sepsis survival. However, further randomized clinical trials are needed to prove the causality [17▪▪].

Before interpretation of plasma vitamin C concentrations in septic patients, accuracy of the sampling and assay techniques should be considered. Inadequate sampling and errors in handling may compromise the results. Plasma vitamin C concentration is probably a fair reflection of whole body vitamin C status [18]. Many analytical techniques are used for the determination of vitamin C in plasma. The most sensitive and selective method is HPLC coupled to an electrochemical detector. This technique is costly and only is available in research laboratories. HPLC with an ordinary ultraviolet light detector is less expensive but it is not practical. Selecting suitable mobile phase, dedicated column, column-conditioning times, procedures to reduce dehydroascorbic acid to ascorbic acid to analyze total vitamin C are analytical concerns [19,20].

SAFETY OF VITAMIN C

Before use of any effective drug in the prevention or treatment of a disease, safety must be weighed against efficacy. When the drug in question is a vitamin, it is more difficult to separate physiological, pharmacological, and toxic doses of it. Vitamin C is essentially a nontoxic vitamin. Minor side effects such as acidosis, oxaluria, renal stones, glycosuria, renal tubular injuries, gastrointestinal disturbances, hypersensitivity reactions, prothrombin and cholesterol disturbances, rebound scurvy, vitamin B12 destruction, fatigue and infertility were reported with vitamin C [21]. Many of these were just reported in earlier studies or case reports and have not been reported in recent controlled trials. Importantly some of them were due to laboratory errors [22]. Repeated unpleasant sensation a few hours after infusion and next morning tiredness have been reported after intravenous administration of vitamin C [23].

Vitamin C can interfere with some laboratory tests involving redox reactions including falsely elevated blood glucose measured by a point of care glucometer [24,25]. Vitamin C can cause falsely elevated serum sodium, potassium, calcium, and creatinine and can result in a false decrease in serum chloride, total bilirubin, uric acid, total cholesterol, triglyceride, ammonia, and lactate [20]. Laboratory errors because of interference with autoanalyzer measuring serum lactate dehydrogenase and transaminases also have been reported [21]. It also can result in false negatives for occult blood testing of stool samples [26].

Ascorbic acid is remarkably safe and nontoxic even at 10–100 times the recommended dietary allowance when taken orally. Generally, adverse effects of high doses of vitamin C (up to 1.5 g/kg three times a week as intravenously) in cancer patients with normal renal function and sufficient glucose-6-phosphate dehydrogenase (G6PD) activity were mild [27,28]. Reactions like localized pain and stinging in the injection site that occur following rapid infusion or using high-osmolar solutions are preventable by adequate hydration before, during, and after the infusion and decrease in the rate of infusion [27]. Most cancer patients tolerated infusion rate of 0.5 g/min of vitamin C. Due to probably uptake by tumor cells, dextrose solution was not recommended as an appropriate diluent of vitamin C in cancer patients [28].

Most recent trials examined the safety of short-term uses of high doses of vitamin C. In one trial high doses of vitamin C for a long time (75–100 g/infusion,

twice a week for 1 year) were safe [29]. As the applied dose and duration of administration of vitamin C in sepsis are lower and shorter than those used in cancer patients, it seems that it is relatively safe for this population. The main concerns to keep in mind regarding vitamin C safety are addressed in below.

Kidney stone

As vitamin C is partly converted to oxalate, it has been frequently claimed that the use of high doses of vitamin C could increase the risk of calcium oxalate kidney stones. The rate-limiting intestinal ascorbic acid transport makes it improbable that oral doses of higher than 500 mg/day proportionately increase the risk of oxalate nephropathy [30▪]. However, intravenous administration of vitamin C bypasses the rate-limiting barrier. Oxalic acid is an end-product of vitamin C oxidation, and oxalate nephropathy has been reported after intravenous administration of vitamin C in patients with renal dysfunction [31▪]. In patients with normal renal function, only about 0.5% of the dose (1.5 g/kg intravenously) was detected as oxalic acid in the urine samples. Because of the possibility of ex-vivo conversion of vitamin C to oxalate, it is also suggested that hyperoxaluria associated with the use of high doses of ascorbic acid could be primarily due to a laboratory artifact [32]. Even if a small increase in urinary oxalate occurs, it might be counter-balanced, as vitamin C binds with calcium and decreases its availability to form calcium oxalate crystals. Vitamin C also causes a small decrease in urinary pH and consequently facilitates the calcium oxalate solubility. Various studies have shown that vitamin C neither increased and nor decreased risk of nephrolithiasis [33].

Dose and duration of administration usually determine vitamin C-induced oxalate nephropathy. Most of the oxalate nephropathy episodes were reported following high doses and long-term uses of vitamin C in patients with baseline renal dysfunction. However, some cases with normal renal function also experienced oxalate nephropathy following short-term uses of vitamin C [34]. Also renal failure episodes in patients who received a single intravenous of high doses of vitamin C (2.5–45 g) have been documented [35▪]. Recently, two cases of severe oxalate nephropathy following administration of high doses of vitamin C were reported [36]. A septic patient who received approximately 30 g of vitamin C over 2.5 months, developed oxalate nephropathy [37]. These reports raise the concern regarding severe and potentially irreversible renal impairment associated with high doses of vitamin C even in patients with normal baseline renal function.

Marik and Hooper [13] are convinced that the suggested vitamin C dose of 1.5 g every 6 h is safe. High baseline serum oxalate levels in three patients decreased following administration of vitamin C that could be due to the attenuation of the inflammatory responses [11]. Thiamine pyrophosphate is an important coenzyme required for the function of glyoxylate aminotransferase that catalyzes the breakdown of glyoxalate to carbon dioxide instead of oxalate. Thus, the inclusion of thiamin in the combination proposed by Marik might prevent the oxaluria [38]. Lamarche *et al.* [34] suggested that empiric treatment with prednisone might improve the prognosis of oxalate nephropathy. None of the cases of oxalate nephropathy associated with ascorbic acid received steroids. Hydrocortisone in the combination proposed by Marik might play a role in the prevention of oxalate nephropathy by subsiding the inflammation. Further studies needed to define the preventive role of thiamin and hydrocortisone.

Hemolysis in glucose-6-phosphate dehydrogenase deficiency

Septic patients are vulnerable to hemolysis due to severity of acute illnesses, baseline diseases, concomitant organ failure, fever, and drugs. This requires a thorough medication review to identify substances that are usually considered safe like vitamin C. Though the hemolysis associated with vitamin C is dose-related, safe doses in these patients are not defined. Doses of 3–80 g have been reported in the literature [39]. Because individuals with baseline glucose 6-phosphate dehydrogenase deficiency are at risk, G6PD status should be tested in septic patients before use of high-dose of vitamin C.

Oxidant and pro-oxidant effects

Vitamin C not only is an antioxidant but also due to its pro-oxidant properties and increase in free radicals might show cytotoxic effects at high serum concentrations. Redox potential of the cellular environment, presence of metals and local concentration of ascorbate may determine the oxidant or pro-oxidant effects of vitamin C. This may explain the observed specific pro-oxidant activities of high-dose of vitamin C in metal rich malignant cells [40]. Increased mutagenesis associated with vitamin C has been reported. However, the presence of metal ions is required for this effect. It should be noted that metal ions are sequestered by binding proteins in the body and thus are not available as in ex-vivo systems [41▪].

It is also important to note that free iron is an abundant ion in myocardial and endothelial cells. Hence, during ischemia a large number of free iron ions may be released in serum and saturate the iron binding capacity. This is so critical in sepsis particularly in patients with hemochromatosis [1].

It has been proposed that in some conditions, vitamin C alone or mixed with *N*-acetyl-cysteine could act as a pro-oxidant (Fenton reaction). Vitamin C (12.5 mg/kg) and N-Acetyl Cysteine (10 mg/kg) for 7 days transiently increased tissue damage and oxidative stress after an acute muscle injury induced by eccentric exercise [42].

VITAMIN C SAFETY IN SEPSIS

The severity of acute illnesses, baseline diseases and medications predispose critically ill patients to adverse effects of any new intervention. During the phase 1 trial in severe sepsis testing very high (200 mg/kg) and high (25 mg/kg) doses of intravenous vitamin C delivered for 4 days, no identifiable side effect was detected in two cohorts of eight patients [43]. Zabet *et al.* reported no ascorbic acid related adverse event in 14 patients with septic shock treated with 100 mg/kg/day of intravenous vitamin C. However, in this study patients with bilateral ureteric obstruction, chronic hemodialysis, iron overload, oxalate stone formers, hemochromatosis, and G6PD deficiency were excluded [44]. Kim *et al.* [45] found no side effect in 53 patients treated with hydrocortisone, ascorbic acid, and thiamin (HAT). Marik *et al.* [46] reported no significant side effect in 47 patients treated with HAT for severe sepsis and septic shock. Side effects of vitamin C were not assessed in other studies [47–50].

Currently, 25 clinical trials have been registered at clinicalTrials.gov to evaluate the efficacy of high doses of vitamin C or HAT in adult septic patients. Of these, four trials (NCT02455180, NCT01434121, NCT02734147, and NCT02106975) have been completed, but not published yet. One trial (NCT03335124) was terminated due to insufficient enrollment. Like the published trials, safety of vitamin C is not primary outcome in ongoing trials. HYVITS trial is evaluating HAT efficacy in septic shock. This trial (registered as NCT03380507) will evaluate the incidence of nephrolithiasis, hypokalemia, hemolysis, hyperthermia, and gastrointestinal bleeding as secondary outcome. CITRIS-AH trial (NCT03829683) is evaluating vitamin C efficacy in sepsis and alcoholic hepatitis. Urine pH and microscopy assessment are considered in this trail.

CONCLUSION

Due to severity of acute illnesses, baseline diseases, organ failure, and medications, septic patients are more vulnerable to side effects of any new intervention. Data regarding safety of high doses of vitamin C in sepsis are scant. Most evidences came from other populations. No serious safety concerns have not been reported, and are of course not primary endpoints in sepsis trials. Until more data become available, caution should be applied to use of high doses of vitamin C in septic patients with hemochromatosis, G6PD deficiency, kidney dysfunction, renal stone, or oxaluria and pediatrics. Vitamin C seems to be a safe intervention for septic patients without these problems. Adequate hydration, appropriate dilution and slow rate of infusion should be considered for all patients who are candidate to receive high doses of vitamin C.

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Conflicts of interest

There are no conflicts of interest.

REFERENCES AND RECOMMENDED READING

Papers of particular interest, published within the annual period of review, have been highlighted as:

- ■ of special interest
- ■■ of outstanding interest

1. Spoelstra-de Man AM, Elbers PW, Oudemans-van Straaten HM. Making sense of early high-dose intravenous vitamin C in ischemia/reperfusion injury. Crit Care 2018; 22:70.
2. Gotts JE, Matthay MA. Sepsis: pathophysiology and clinical management. BMJ 2016; 353:i1585.
3. Oudemans-van Straaten HM, Elbers PW, Spoelstra-de Man AM. How to give vitamin C a cautious but fair chance in severe sepsis. Chest 2017; 151:1199–1200.
4. Marik PE. Patterns of death in patients with sepsis and the use of hydrocortisone, ascorbic acid, and thiamine to prevent these deaths. Surg Infect (Larchmt) 2018; 19:812–820.
5. Hill A, Wendt S, Benstoem C, *et al.* Vitamin C to improve organ dysfunction in cardiac surgery patients – review and pragmatic approach. Nutrients 2018; 10:974.
6. Teng J, Pourmand A, Mazer-Amirshahi M. Vitamin C: the next step in sepsis management? J Crit Care 2018; 43:230–234.
7. Lamontagne F. Vitamin C for the critically ill: is the evidence strong enough? Nutrition 2018; 60:185–190.
8. Hemilä H. Vitamin C and infections. Nutrients 2017; 9:339.
9. Mantzarlis K, Tsolaki V, Zakynthinos E. Role of oxidative stress and mitochondrial dysfunction in sepsis and potential therapies. Oxid Med Cell Longev 2017; 2017:1–10.
10. Badeaux JE, Martin JB. Emerging adjunctive approach for the treatment of sepsis. Crit Care Nurs Clin North Am 2018; 30:343–351.
11. Marik PE. Vitamin C for the treatment of sepsis: the scientific rationale. Pharmacol Ther 2018; 189:63–70.
12. de Grooth H-J, Zandvliet AS, Oudemans-van Straaten HM, *et al.* Vitamin C pharmacokinetics in critically ill patients. Chest 2018; 153:1368–1377.
13. Marik PE, Hooper MH. Doctor – your septic patients have scurvy. Crit Care 2018; 22:22–23.
14. Rosini J, Arnold R, Schuchardt B, *et al.* High dose intravenous ascorbic acid in severe sepsis. Acad Emerg Med 2018; 25(S1):S108–S109.

15. Spoelstra-De Man AME, Elbers PWG, Oudemans-Van Straaten HM. Vitamin ■ C: should we supplement? Curr Opin Crit Care 2018; 24:248–255.
Role of supplemental vitamin C.
16. Amrein K, Oudemans-van Straaten HM, Berger MM. Vitamin therapy in ■ critically ill patients: focus on thiamine, vitamin C, and vitamin D. Intensive Care Med 2018; 44:1940–1944.
Role of vitamin C in ischemia/reperfusion injury.
17. Li J. Evidence is stronger than you think: a meta-analysis of vitamin C use in ■■ patients with sepsis. Crit Care 2018; 22:1–4.
Metaanalysis of vitamin C in sepsis.
18. Dehghan M, Akhtar-Danesh N, McMillan CR, Thabane L. Is plasma vitamin C an appropriate biomarker of vitamin C intake? A systematic review and meta-analysis. Nutr J 2007; 6:41.
19. Robitaille L, Hoffer LJ. A simple method for plasma total vitamin C analysis suitable for routine clinical laboratory use. Nutr J 2016; 15:1–9.
20. Meng QH, Irwin WC, Fesser J, Massey KL. Interference of ascorbic acid with chemical analytes. Ann Clin Biochem 2005; 42:475–477.
21. Barness LA. Safety considerations with high ascorbic acid dosage. Ann New York Acad Sci 1975; 258:523–528.
22. Sies R, Paoletti H, Poli J, *et al.* Vitamin C: the state of the art in disease prevention sixty years after the Noble Prize. Berlin Heidelberg: Springer; 1998 ; 125–132.
23. Vollbracht C, Raithel M, Krick B, *et al.* Intravenous vitamin C in the treatment of allergies: an interim subgroup analysis of a long-term observational study. J Int Med Res 2018; 46:3640–3655.
24. Hager DN, Martin GS, Sevransky JE, Hooper MH. Glucometry when using vitamin C in sepsis. Chest 2018; 154:228–229.
25. Flannery AH, Bastin MLT, Magee CA, Bensadoun ES. Vitamin C in sepsis: when it seems too sweet, it might (literally) be. Chest 2017; 152:450–451.
26. Fletcher RH. Diet for fecal occult blood test screening: help or harm? Eff Clin Pract 2001; 4:180–182.
27. Melnychuk D, Miller WH, Rousseau C, *et al.* Phase I clinical trial of i.v. ascorbic acid in advanced malignancy. Ann Oncol 2008; 19:1969–1974.
28. Padayatty SJ, Sun AY, Chen Q, *et al.* Vitamin C: intravenous use by complementary and alternative medicine practitioners and adverse effects. PLoS One 2010; 5:e11414.
29. Polireddy K, Levine M, Ma Y, *et al.* High-dose parenteral ascorbate enhanced chemosensitivity of ovarian cancer and reduced toxicity of chemotherapy. Sci Transl Med 2014; 6:222ra18–1222ra.
30. Padayatty SJ, Sun H, Wang Y, *et al.* Brief communication vitamin c pharma- ■ cokinetics: implications for oral and intravenous use. Ann Intern Med 2004; 140:533–538.
Vitamin C Pharmacokinetic.
31. Cossey LN, Rahim F, Larsen CP. Oxalate nephropathy and intravenous ■ vitamin C. Am J Kidney Dis 2013; 61:1032–1035.
Oxalate nephropathy of vitamin C.
32. Robitaille L, Mamer OA, Miller WH, *et al.* Oxalic acid excretion after intravenous ascorbic acid administration. Metabolism 2009; 58:263–269.
33. Ferraro PM, Curhan GC, Gambaro G, Taylor EN. Total, dietary, and supplemental vitamin C intake and risk of incident kidney stones. Am J Kidney Dis 2016; 67:400–407.
34. Lamarche J, Nair R, Peguero A, Courville C. Vitamin C-induced oxalate nephropathy. Int J Nephrol 2011; 2011:1–4.
35. Shibuya N, Humphers JM, Agarwal MR, Jupiter DC. Efficacy and safety of ■ high-dose vitamin C on complex regional pain syndrome in extremity trauma and surgery – systematic review and meta-analysis. J Foot Ankle Surg 2013; 52:62–66.
Meta-analysis regarding safety of vitamin C.
36. Doucet B, Noble E, Gray N. High dose vitamin c (ascorbic acid) causing renal failure due to oxalate nephropathy. Nephrology 2018; 23:71.
37. Colliou E, Mari A, Delas A, *et al.* Oxalate nephropathy following vitamin C intake within intensive care unit. Clin Nephrol 2017; 88:354–358.
38. Moskowitz A, Andersen LW, Huang DT, *et al.* Ascorbic acid, corticosteroids, and thiamine in sepsis: a review of the biologic rationale and the present state of clinical evaluation. Crit Care 2018; 22:283.
39. Lee SWH, Lai NM, Chaiyakunapruk N, Chong DWK. Adverse effects of herbal or dietary supplements in G6PD deficiency: a systematic review. Br J Clin Pharmacol 2017; 83:172–179.
40. Tóth SZ, Lőrincz T, Szarka A. Concentration does matter: the beneficial and potentially harmful effects of ascorbate in humans and plants. Antioxid Redox Signal 2018; 29:1516–1533.
41. Garewal HS, Diplock AT. How 'safe' are antioxidant vitamins? Drug Saf 1995; ■ 13:8–14.
Safety of antioxidant vitamins.
42. Childs A, Jacobs C, Kaminski T, *et al.* Supplementation with vitamin C and *N*-acetyl-cysteine increases oxidative stress in humans after an acute muscle injury induced by eccentric exercise. Free Radic Biol Med 2001; 31:745–753.
43. Syed AA, Knowlson S, Sculthorpe R, *et al.* Phase I safety trial of intravenous ascorbic acid in patients with severe sepsis. J Transl Med 2014; 12:32.
44. Zabet M, Mohammadi M, Ramezani M, Khalili H. Effect of high-dose ascorbic acid on vasopressor's requirement in septic shock. J Res Pharm Pract 2016; 5:94.
45. Kim WY, Jo EJ, Eom JS, *et al.* Combined vitamin C, hydrocortisone, and thiamine therapy for patients with severe pneumonia who were admitted to the intensive care unit: propensity score-based analysis of a before-after cohort study. J Crit Car 2018; 47:211–218.
46. Marik PE, Khangoora V, Rivera R, *et al.* Hydrocortisone, vitamin C, and thiamine for the treatment of severe sepsis and septic shock a retrospective before-after study. Chest 2018; 53:783–784.
47. Shin TG, Kim YJ, Ryoo SM, *et al.* Early vitamin C and thiamine administration to patients with septic shock in emergency departments: propensity score-based analysis of a before-and-after cohort study. J Clin Med 2019; 8:; 102. doi: 10.3390/jcm8010102.
48. Ferrón-Celma I, Mansilla A, Hassan L, *et al.* Effect of vitamin C administration on neutrophil apoptosis in septic patients after abdominal surgery. J Surg Res 2009; 153:224–230.
49. Natarajan R. Impact of intravenous ascorbic acid infusion on novel biomarkers in patients with severe sepsis. J Pulm Respir Med 2015; 4:4–11.
50. Balakrishnan M, Gandhi H, Shah K, *et al.* Hydrocortisone, vitamin C and thiamine for the treatment of sepsis and septic shock following cardiac surgery. Indian J Anaesth 2018; 62:934–939.