



Vitamin C: should we supplement?

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Purpose of review

Hypovitaminosis C and vitamin C deficiency are very common in critically ill patients due to increased needs and decreased intake. Because vitamin C has pleiotropic functions, deficiency can aggravate the severity of illness and hamper recovery.

Recent findings

Vitamin C is a key circulating antioxidant with anti-inflammatory and immune-supporting effects, and a cofactor for important mono and dioxygenase enzymes. An increasing number of preclinical studies in trauma, ischemia/reperfusion, and sepsis models show that vitamin C administered at pharmacological doses attenuates oxidative stress and inflammation, and restores endothelial and organ function. Older studies showed less organ dysfunction when vitamin C was administered in repletion dose (2–3 g intravenous vitamin C/day). Recent small controlled studies using pharmacological doses (6–16 g/day) suggest that vitamin C reduces vasopressor support and organ dysfunction, and may even decrease mortality.

Summary

A short course of intravenous vitamin C in pharmacological dose seems a promising, well tolerated, and cheap adjuvant therapy to modulate the overwhelming oxidative stress in severe sepsis, trauma, and reperfusion after ischemia. Large randomized controlled trials are necessary to provide more evidence before wide-scale implementation can be recommended.

Keywords

antioxidant, critical care, multiple organ dysfunction, oxidative stress, vitamin C

INTRODUCTION

Many of us will associate vitamin C deficiency with sailors dying from scurvy during the 'Age of Exploration.' However, it has now become evident that vitamin C deficiency is certainly not a thing of the past, but develops during extreme circumstances. In fact, deficiency (normal plasma vitamin C levels $\geq 23 \mu\text{mol/l}$) is frequently encountered in critically ill patients [1[•]]. A recent study found that 88% of the septic patients had hypovitaminosis C (i.e. $< 23 \mu\text{mol/l}$), whereas 38% had scurvy levels (i.e. $< 11 \mu\text{mol/l}$) [2^{••}]. The physiologic importance of vitamin C can be observed in pond turtles, which possess particularly high concentrations of vitamin C in the brain. These animals exhibit a high tolerance for oxygen depletion during diving, and vitamin C may help to prevent oxidative damage to neurons during re-oxygenation following a hypoxic period [1[•]]. In analogy to these freshwater turtles [3], evidence suggests that vitamin C could protect patients against overwhelming oxidative stress, and that early administration might improve outcome [4].

WHY IS VITAMIN C DEFICIENT?

The acute vitamin C deficiency is probably caused by increased metabolic consumption due to critically ill-induced oxidative stress with reduced recycling of dehydroascorbic acid (DHA), oxidized vitamin C. Most animals are capable of synthesizing vitamin C from glucose-6-phosphate, and their endogenous synthesis increases during stress [5].

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KEY POINTS

- Vitamin C deficiency is frequently encountered in critically ill patients due to increased needs, and may persist, despite (par)enteral nutrition.
- Vitamin C has pleiotropic effects as key circulating antioxidant with anti-inflammatory and immune-supporting effects, and as cofactor for mono and dioxygenase enzymes.
- An intravenous dose of 2–3 g/day is needed to restore normal plasma concentrations (repletion dose), as enteral uptake is insufficient due to maximum enteral absorption capacity.
- Vitamin C in repletion dose reduced organ failure in older studies, and recent small controlled studies suggest that vitamin C used in pharmacological doses (6–16 g/day) reduces vasopressor support, fastens recovery from organ failure, and may even reduce mortality.
- A short course of pharmacological dose vitamin C seems well tolerated, and may, despite increased oxalate excretion, even improve kidney function.

However, humans have lost the ability to synthesize vitamin C due to mutations in the L-gulono- γ -lacton oxidase which encodes the terminal step of the vitamin C synthesis. During normal circumstances, dietary intake is sufficient to keep vitamin C levels within normal range. However, during critical illness, increased demands may lead to insufficiency. Lowest vitamin C levels are seen in patients with multiple organ failure [6], and plasma vitamin C levels are inversely related to sequential organ failure assessment (SOFA) scores and mortality [7]. Because vitamin C has pleiotropic functions, deficiency can aggravate the severity of illness and hamper recovery. Therefore repletion, and perhaps pharmacological dosing of vitamin C, could be an effective adjuvant therapy in conditions with excessive oxidative stress. Under these circumstances, it is essential that vitamin C is administered intravenously, because during critical illness, enteral uptake is both unpredictable and limited. In this narrative review, we will summarize the current knowledge of the pivotal role of vitamin C in critically ill patients. To meet this objective, we will discuss the clinical and preclinical studies published in the past 5 years investigating repletion and pharmacological dosing of intravenous vitamin C as adjuvant therapy in trauma, ischemia/reperfusion injury, and sepsis.

PATHOPHYSIOLOGY

In multiple critical conditions, such as trauma, ischemia/reperfusion injury, and sepsis, oxidative

stress plays a crucial role. The original insult induces a progressive inflammatory response by activation of nuclear kappa-B with release of cytokines and production of multiple reactive oxygen species (ROS) by various inter-related pathways [8,9] (Fig. 1) and leading to uncoupling of mitochondrial phosphorylation, activation of nicotinamide adenine dinucleotide phosphate oxidase, lipoxygenase, cyclooxygenase and inducible nitric oxide synthase (iNOS), and oxidation of catecholamines. The abundance of ROS, especially when insufficiently opposed by antioxidants such as vitamin C, leads to cellular injury, widespread endothelial dysfunction, and progressive organ dysfunction.

WHY VITAMIN C COULD WORK

During critical illness, vitamin C has pleiotropic effects as key circulating antioxidant with anti-inflammatory and immune-supporting effects, and as cofactor for mono and dioxygenase enzymes (Table 1). All of these crucial functions are based on electron donation. The pleiotropic action could decrease cellular and organ injury.

PHARMACOKINETICS

Dietary vitamin C is absorbed via the saturable mucosal sodium-dependent vitamin C transporter 1 (SCVC1) with maximum plasma vitamin C levels after enteral intake of 220 $\mu\text{mol/l}$ in volunteers. Supraphysiological levels can only be attained by intravenous vitamin C supplementation [17]. Vitamin C is filtered by the glomerulus and actively reabsorbed in the proximal tubule (SVCT1). Urine excretion of vitamin C starts from plasma levels around 55 $\mu\text{mol/l}$. Tubular reabsorption is saturable. Vitamin C is actively transported into the tissue cells (SCVC2), leading to higher intracellular concentrations than in plasma, especially in activated leucocytes and in neurons protecting them against ROS. Vitamin C enters the brain both via SCVT2 and as DHA via glucose transporter 1.

In critically ill patients enteral uptake is insufficient to normalize plasma levels, due to saturable enteral transport, diminished mucosal function, and increased needs. Deficiency persists, despite receiving recommended intakes by (par) enteral nutrition [1[•],2^{••},6]. To restore plasma levels in critically ill patients, a minimum of 2–3 g intravenous (i.v.) vitamin C is necessary [18^{••},19]. With 10 g, and respectively, approximately 16 g i.v. vitamin C/day [18^{••},20] plasma levels of above 1000 $\mu\text{mol/l}$ can be achieved with a linear dose-response relationship [18^{••}].

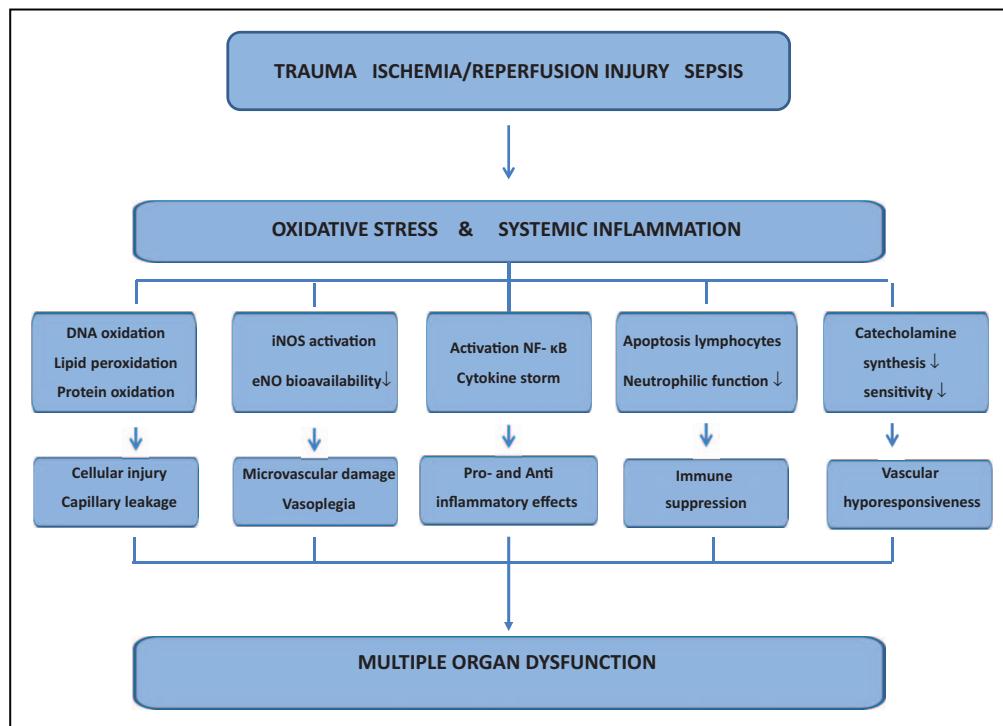


FIGURE 1. Pathophysiological pathways after a primary insult (trauma, ischemia/reperfusion injury, sepsis) which induces oxidative stress and systemic inflammation, and can lead to remote organ dysfunction. IL-1 β , interleukin-1 β ; IL-6, interleukin-6; NF- κ B, nuclear factor- κ B; NO, nitric oxide; TNF- α , tumor necrosis factor- α .

PRECLINICAL STUDIES

Many studies investigating the use of pharmacological doses of vitamin C in preclinical models of sepsis and ischemia/reperfusion showed attenuation of oxidative stress and inflammation restoring endothelial and organ function, as we reviewed in 2014 [11]. Since then, several new relevant studies in preclinical models of trauma, ischemia/reperfusion injury, and sepsis were performed.

In a swine polytrauma model, i.v. vitamin C (50 and 200 mg/kg) significantly reduced proinflammatory mediators [interleukin (IL)-1, IL-8, and plasminogen activator inhibitor-1] and greatly reduced injury of the lung (hemorrhage, septal edema, and inflammation), liver, and kidney (microangiopathy and cellular infiltration) [21].

In a cardiac arrest rat model, vitamin C (50 and 100 mg/kg i.v.) decreased myocardial damage and improved neurological outcome and survival [22]. However, in another study 250 mg/kg vitamin C compromised resuscitability, possibly due to the much higher dose used [23]. In an isolated perfused rat heart and isolated cardiomyocytes vitamin C inhibited ROS generation, reduced infarct area, and improved cardiac function by reducing calcium overload and impeding the opening of the mitochondrial permeability transition pore [24]. In a renal ischemia/reperfusion model in rats, i.v.

50 mg/kg vitamin C reduced renal injury and preserved renal tissue, especially when combined with hydrocortisone [25].

In a cecal ligation/perforation sepsis model, multiple organ dysfunction and mortality were lower in wild-type mice compared to Gulo $-/-$ knockout mice, which are incapable to synthesize vitamin C. Subcutaneous administration of 200 mg/kg vitamin C improved cellular immunosuppression and reduced organ dysfunction and mortality in both Gulo $-/-$ and Gulo $+/+$ mice, supporting additional benefit of supraphysiological plasma vitamin C levels [26 $^{\bullet}$]. In human lung endothelial cells with lipopolysaccharide-induced hyperpermeability vitamin C enhanced endothelial barrier function only in combination with hydrocortisone [27 $^{\bullet}$].

CLINICAL STUDIES

As previously reviewed by us [1 $^{\bullet}$,11], two older studies in trauma patients [one randomized controlled trial (RCT) of 595 patients [28] and one before/after study in 4294 patients [29] using repletion doses of 3 gram i.v. vitamin C/day combined with vitamin E] showed reduced organ dysfunction, length of stay [28,29], and mortality [29]. In this population, no new clinical trials have been performed since. Similarly, in burn patients, no new

Table 1. Pleiotropic effects of vitamin C

Pleiotropic effects	
Antioxidative	
Direct radical scavenger [10▪▪]	Superoxide Peroxynitrite
Reduction of ROS-production [11]	Inhibition of activation of NADPHoxidase Inhibition of activation of xanthine oxidase Reduction of leakage of electrons from the dysfunctional electron transport chain in the mitochondria Inhibition of iNOS expression, preventing abundant NO production and peroxy nitrite generation
Regeneration of antioxidants [12]	α -tocopherol, protecting against lipid peroxidation Glutathione Urate Tetrahydrobiopterin
Anti-inflammatory	Inhibition of NF- κ B, reducing proinflammatory mediators
Immune-supporting [13▪▪]	Improvement of chemotaxis Stimulation interferon production Enhancement of neutrophilic bacterial killing Support of lymphocyte proliferation Modulating regulatory T-cells Inhibiting bacterial replication Production of host defence peptides [14]
Cofactor/cosubstrate biosynthesis [15]	Dopamine Norepinephrine Vasopressin Serotonin Cortisol Collagen
Increase of catecholamine sensitivity	Type IV collagen hydroxylation Oxidative protein folding
Protection microcirculation [11]	Binding to adrenergic receptors
Tightening endothelial barrier	Inhibition PP2A activation, increasing phosphorylated occludin crucial for maintenance of tight junctions Inhibition of apoptosis of endothelial progenitor cells
Improving microcirculatory patency	Inhibition of TNF- α -induced ICAM expression, reducing leucocyte stickiness and sludging
Decrease of endothelial permeability and protection against pathological vasoconstriction	Prevention eNOS uncoupling and eNO depletion
Improvement of wound healing [16]	

eNO, endothelial nitric oxide; eNOS, endothelial nitric oxide synthase; NADPH, nicotinamide adenine dinucleotide phosphate oxidase.

clinical studies have been performed since 2014. That leaves us with two old small studies performed with huge doses of vitamin C (66 mg/kg/h for 24 h) which reduced fluid requirements and increased urine output [30,31].

With regard to ischemia/reperfusion injury no clinical studies have been performed in critically ill patients after cardiac arrest or stroke. Patients

with ST-elevation myocardial infarction receiving i.v. vitamin C prior to percutaneous coronary intervention and achieving plasma levels above 1 mmol/l had significantly better left ventricular function and microvascular function than patients with levels below 1 mmol/l [32]. In a RCT of 532 patients, infusion of 3 g vitamin C before elective percutaneous coronary intervention showed a significant

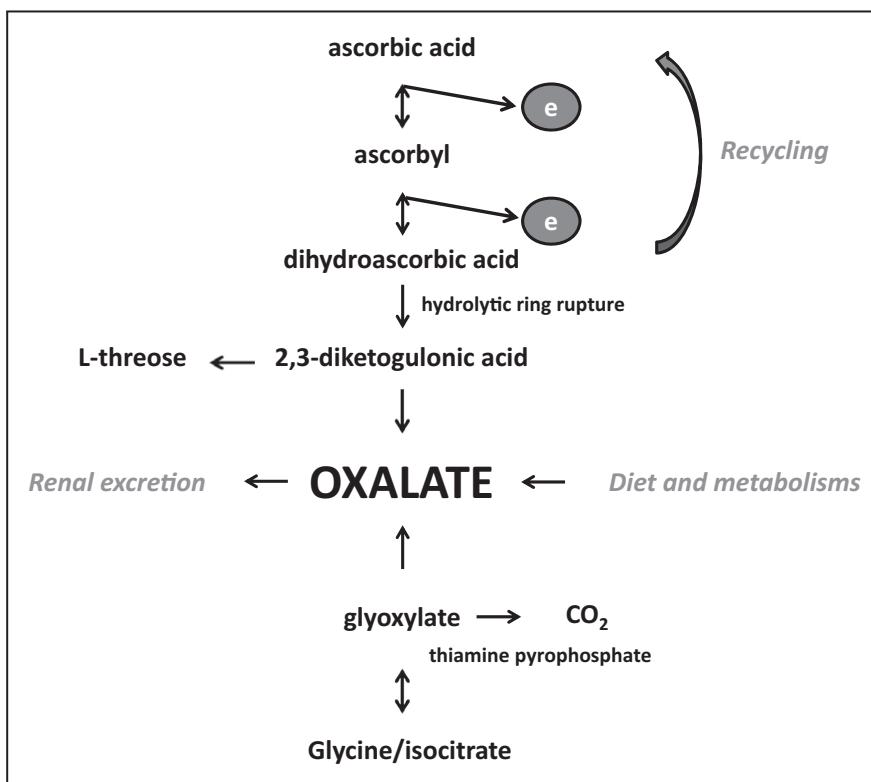


FIGURE 2. Pathways of oxalate biosynthesis.

decrease of myocardial injury and blunted the increase of 8-hydroxy-2-deoxyguanosine – an oxidative stress marker [33].

Several recent clinical studies applying pharmacological doses of vitamin C focussed on sepsis. In a small RCT in 24 patients with severe sepsis and septic shock, 50 and 200 mg/kg/day reduced the inflammatory response, decreased circulating levels of cell-free and mitochondrial DNA, increased levels of antimicrobial proteins [14], and reduced the SOFA score, all to a larger extent in the 200 mg/kg/day group [20]. In second small RCT in 28 surgical ICU patients with septic shock, 100 mg i.v. vitamin C/kg/day reduced vasopressor requirements and mortality [34*]. A very recent before and after study investigating the ‘cocktail’ of vitamin C, hydrocortisone, and thiamine amazed not only the critical care community but also the lay press due to the considerable effect on mortality (40 in the standard care group vs. 8% in the vitamin C/hydrocortisone/thiamine group). In addition, the duration of vasopressor therapy was significantly reduced (54.9 vs. 18.3 h) and SOFA score decreased faster. Importantly, kidney function was better in the vitamin C group, which is reassuring with regard to the potential risk of oxalate nephropathy. However, acknowledged limitations of the study are the low number of patients, the historical

control group (although well matched), and the single-center design [35**].

ADVERSE EFFECTS

Potential side effects of pharmacological doses of i.v. vitamin C are oxalate nephropathy, pro-oxidative activity, and factitious hyperglycemia in point-of-care glucose measurements [36].

Vitamin C is mainly metabolized (reversibly) to DHA and (when not recycled) subsequently to 2,3-diketo-1-gulonic acid and oxalate (Fig. 2). Oxalate is excreted in the urine. In primary hyperoxaluria, oxalate nephropathy takes months to years to develop. Prolonged supplementation of high-dose vitamin C can increase the risk of oxalate nephropathy. In the recent controlled studies in critically ill patients with high doses for a short period, no oxalate nephropathy was reported [1*], and kidney function even improved [35**]. Few case reports describe oxalate nephropathy in burn patients after vitamin C administration (101 and 224 g <24 h) much higher than used in most clinical trials [36].

High concentrations of vitamin C can affect blood glucose measurements by some, not all, point-of-care glucometers, leading to falsely higher

results [37]. This can lead to hypoglycemia if aggressive insulin therapy is erroneously applied. Therefore, glucose measurements after the administration of pharmacological doses of vitamin C should be performed at the central laboratory or with blood gas analysis [38].

Vitamin C can induce pro-oxidative effects. When donating one electron to ROS, vitamin C converts to the ascorbate radical, which can be pro-oxidant, but frequently has substituted a much stronger and unstable radical. Furthermore, vitamin C can reduce the ion status of metals like copper and iron, and by the Fenton reaction lead to production of superoxide and hydrogen peroxide. A recent review showed that vitamin C *in vivo* predominantly reduced oxidative damage, despite the described *in vitro* pro-oxidative effects [39]. High-dose i.v. vitamin C should be avoided in patients with glucose-6-phosphate deficiency, who can develop hemolysis.

SYNERGISM WITH THIAMINE AND HYDROCORTISONE

Vitamin C can reverse the oxidation of the glucocorticoid receptor and restore the activity of glucocorticoids. *Vice versa*, glucocorticoids stimulate the expression of SVCT2, which actively transports vitamin C into the tissue cells, but is down-regulated in sepsis.

Thiamine deficiency frequently occurs in septic patients due to increased consumption [40] and can enhance reduction of glyoxylate to oxalate instead of oxidation to CO₂ (Fig. 2), increasing hyperoxaluria. In addition, thiamine is an important cofactor in the energy metabolism, and thiamine deficiency causes mitochondrial dysfunction and oxidative stress [41,42]. Supplementation of thiamine could reduce hyperoxaluria and act synergistically with hydrocortisone and vitamin C to reduce organ dysfunction and improve outcome [35^{**}].

DISCUSSION

When considering all the available evidence, i.v. vitamin C – in repletion dose, but maybe even more in pharmacological dose – is a promising potential adjuvant therapy for critical illnesses with increased oxidative stress, such as trauma, ischemia/reperfusion injury, and sepsis. There is a good pathophysiological rationale supported by an increasing number of (pre)clinical studies.

Preclinical studies, however, do not show unequivocal results, and the clinical studies are mostly small, single-centered, and not all are randomized. Doses differ widely and are often combined with other antioxidants or hydrocortisone. Therefore, requests for immediate wide-scale implementation of

vitamin C in pharmacological doses should not be honored at this time. Several large, double-blinded RCTs in the sepsis population are under way, but other ICU populations might benefit, such as patients after cardiac arrest, trauma, or burn. They are necessary to provide more evidence.

If vitamin C does indeed benefit critically ill patients, there still remain many unanswered questions such as the follows:

- (1) Is my patient deficient? First of all, we need a reliable screening of vitamin C status for clinical practice. At present, determination of plasma vitamin C levels is complicated and expensive, and not available for daily practice.
- (2) Should we provide repletion or pharmacological doses? There are no comparative studies showing that 1.5 g q 6 hourly is optimal as was recently suggested [35^{**}]. Because pharmacological doses are possibly needed to optimize the antioxidant effects of vitamin C [43], the clinical effect of these doses might be stronger [20,32,34^{*},35^{**}]. However, large studies on side effects are not available.
- (3) What is the optimal timing and duration of supplementation? Probably, vitamin C should be administered as soon as possible after the primary insult, when oxidative stress is maximal. The optimal duration probably differs per patient. We think that high-dose vitamin C should be stopped after the acute phase to allow the beneficial signaling function of ROS necessary for cell survival.
- (4) Should we use bolus or continuous administration? The antioxidant effect is dose-related, thus temporarily high peaks might be beneficial.
- (5) What is the relevance of co-administration of thiamine and hydrocortisone? Pathophysiological, this is plausible in septic patients, but no data are available for patients after trauma or cardiac arrest. At this moment, at least eight RCTs are being performed with either vitamin C alone, or combined with hydrocortisone or thiamine (ClinicalTrials.gov), which will answer some of these questions.

CONCLUSION

Many critically ill patients, especially those exhibiting oxidative stress, are vitamin C-deficient, because needs are increased and intake diminished. An intravenous dose of 2–3 g/day is needed to restore normal plasma concentrations, as enteral uptake is insufficient due to maximum enteral absorption capacity. Several older studies suggest less organ failure when vitamin C is administered in repletion dose. Some

recent small controlled studies suggest that vitamin C used in pharmacological doses (6–16 g/day) reduces vasopressor support, fastens recovery from organ failure, and may even reduce mortality. In addition, it may, despite increased oxalate excretion, even improve kidney function. Whether the combination with thiamine and hydrocortisone is even more beneficial needs to be confirmed. Large RCTs are necessary to provide more evidence and safety data before wide-scale implementation can be recommended. Up to now, a short course of vitamin C seems well tolerated, making this cheap and widely available substance extremely promising to modulate the overwhelming oxidative stress in severe sepsis, trauma, and reperfusion after ischemia.

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Conflicts of interest

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