CHEST

How to Give Vitamin C a Cautious but Fair Chance in Severe Sepsis

Heleen M. Oudemans-van Straaten, MD, PhD
Paul W. G. Elbers, ME, PhD
Angélique M. E. Spoelstra-de Man, MD, PhD
Amsterdam, The Netherlands

PODCAST

Overwhelming inflammation and oxidative stress contribute to the high morbidity and mortality of sepsis by causing vasoplegia, capillary leakage, and organ failure. This provided the strong rationale for Paul Marik's[1] group to target both uncontrolled inflammation and oxidative stress in an attempt to improve patient outcome. In their provocative before and after study, they administered a combination of IV vitamin C, hydrocortisone, and thiamine in the early phase of severe sepsis and found a considerable decrease in organ failure and mortality. Results are reported in this issue of *CHEST*.[1]

The study included 47 consecutive patients with a primary diagnosis of severe sepsis or septic shock and a procalcitonin level of 2 ng/mL or higher and compared this cohort with a control cohort from 7 months earlier. The study intervention included IV vitamin C (1.5 g every 6 h) and IV thiamine (200 mg every 12 h) as well as IV hydrocortisone (50 mg every 6 h). During the control period, 60% of patients also received IV hydrocortisone (50 mg every 6 h) but no supplemental vitamin C or thiamine. The study cocktail was administered within 24 h of ICU admission. The hospital mortality was significantly lower in the treatment group (8.5%) than in the control group (40.4%). The propensity adjusted OR of mortality in the study patients was 0.13 (95% CI, 0.04-0.48). The duration of vasopressor support was reduced by two-thirds, the 72-h delta Sequential Organ Failure Assessment score was reduced by 82%, and the need for renal replacement therapy declined from 37% to 10%. None of the patients in the treatment group experienced progressive organ failure.

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AFFILIATIONS: Department of Intensive Care, VU University Medical Centre.

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CORRESPONDENCE TO: Heleen M. Oudemans-van Straaten, MD, PhD, Department of Intensive Care, VU University Medical Center, De Boelelaan 1117, 1081 HV Amsterdam, The Netherlands; e-mail: hmoudemans@gmail.com

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Why This Combination?

Hydrocortisone and vitamin C act synergistically on multiple sites in the inflammatory cascade.[1-4] In addition, hydrocortisone facilitates the uptake of vitamin C into the cell by restoring the cytokine-induced downregulation of the vitamin C transporter, whereas vitamin C restores the sensitivity of the glucocorticoid receptor.[1] Thiamine was added to reduce the risk of renal oxalate crystallization (see further on).

The Primary Circulating Antioxidant

During sepsis, reactive oxygen species (ROS) are produced in neutrophils. ROS not only kill invading microorganisms but also cause collateral damage to host cells. Vitamin C is the only antioxidant in plasma able to completely prevent neutrophil-induced lipid oxidation.[5] Vitamin C also prevents the depletion of other circulatory antioxidants such as lipid-soluble vitamin E and glutathione, although this is not the case in reverse. However, when consumed, plasma vitamin C becomes rapidly depleted on neutrophil activation.[4,5] *Early* IV supplementation is therefore needed to limit oxidation of lipids, proteins, and DNA.

Protection of the Circulation

Preclinical and clinical studies have shown that vitamin C protects against the loss of the endothelial barrier and microcirculation.[3,4] In addition, vitamin C may increase vasomotor responsiveness by increasing endogenous synthesis of norepinephrine and vasopressin.[6]

Host Defense and Wound Healing

Although glucocorticoids predominantly have antiinflammatory effects, vitamin C reduces oxidant damage and can increase host defenses by improving macrophage and T-cell function.[2,7] Vitamin C is an

essential cofactor in the biosynthesis of collagen and thereby crucial for the firmness of blood vessels. Moreover, vitamin C facilitates wound healing beyond its role in collagen metabolism and blood supply.[8]

Optimal Dose and Route

The optimal dose of vitamin C in the critically ill population is not known. It also is not known whether we should aim at normal or temporarily supernormal plasma concentrations to achieve more antioxidant effects.[2,7] Pharmacokinetic data in critically ill patients are scarce. However, enteral administration is ineffective during critical illness as shown by persistently subnormal plasma concentrations after administering 600 mg vitamin C daily for 8 days.[9] An IV dose of 2 to 3 g/d seems necessary to reach normal plasma concentrations (50-70 μM),[10-12] whereas super-high plasma concentrations can be obtained with dosages of 200 mg/kg/d[11] or 10 g/d.[12] In a phase I safety trial in patients with sepsis, high plasma concentrations were associated with an earlier decline in the Sequential Organ Failure Assessment score and procalcitonin concentrations.[11] With continuous infusion, urinary vitamin C loss and oxalate excretion seem to be lower, whereas a higher proportion of vitamin C remains in the body.[12] Beneficial effects on organ dysfunction or length of ICU support were reported with IV doses between 1,000 mg and up to 200 mg/kg/d.[4,11] The concomitant use of hydrocortisone generally was not mentioned. Altogether, a dose finding is needed.

Negative Image

Despite a huge amount of evidence on the protective effect of vitamin C,[2-4] the administration of vitamin C in higher than the so-called daily recommended dose is often qualified as quackery. Opponents refer to Linus Pauling, who was Nobel Prize winner twice but later in his life persevered in his beliefs that vitamin C taken daily was a panacea and had the miraculous property to prolong life and that mega doses could cure cancer, negating numerous negative studies. A second objection comes from nephrologists pointing to the renal crystallization of oxalate being produced during vitamin C metabolism. However, whether short-term, high-dose administration in the setting of hemodynamic and fluid monitoring will lead to renal oxalate crystallization has not been investigated. Based on physiological reasoning, Marik et al[1] added thiamine to reduce this risk. Thiamine is a coenzyme to glyoxylate aminotransferase, which promotes the oxidation of glyoxylate (a metabolite of vitamin C) to carbon dioxide (instead of oxalate). *Post aut propter*, Marik et al[1] found renal benefit, not harm.

How to Proceed?

The pathophysiology of sepsis reminds us that high-dose IV vitamin C should probably be limited to the very early phase of severe sepsis or septic shock because in the long run, low levels of ROS are crucial for intracellular signaling. To avoid the Linus Pauling trap, pragmatic multicenter trials are needed to confirm this benefit and to exclude unforeseen harm as was seen in previous sepsis trials using promising drugs. Studies should also determine optimal dose and treatment duration, whether normal or temporarily supernormal plasma concentrations should be obtained, whether intermittent (high peak concentrations) or continuous dosing (less renal excretion of vitamin C and oxalate) performs better, whether coadministration of thiamine reduces oxalate excretion, and finally whether the combination with hydrocortisone acts synergistically.

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