Nutrition & Food Science
International Journal
ISSN 2474-767X

Juniper Publishers
key to the Researchers

Review Article
Volume 5 Issue 1 – February 2018
DOI: 10.19080/NFSIJ.2018.05.555654

Nutri Food Sci Int J

The Pro and Con Argument for use of Vitamin C in Critically Ill Patients

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Submission: January 02, 2018; **Published:** February 06, 2018

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Abstract

Vitamin C will certainly end 2017 on a high note and with more attention for the age-old cure of the common cold than it has received in many preceding years. This may very well be deserved praise and usher in a new era of treatment for patients with sepsis. However, previous randomized controlled trials of anti-oxidant combinations (which included vitamin C) do not support the new wave of enthusiasm for vitamin C. Despite this use of vitamin C has increased and many clinicians are excited about the potential benefits. This article presents a pro and con argument regarding vitamin C in the critically ill patient.

PRO

Critically ill patients are often deficient in vitamin C. Prior research has showed that the median concentration of vitamin C (ascorbic acid and dehydroascorbic acid) in critically patients is less than 25% of healthy control subjects [1]. Humans are incapable of synthesizing vitamin C and rely on exogenous sources [2]. Given the lack of synthesis and overall deficit in critically ill patients doses of up to 3 grams per day are often needed to achieve significant increase in serum levels [3]. The role of vitamins C in critically ill patients is primarily based on its ability to mitigate damage from reactive oxygen species. It has also been studied in several critically ill patient populations with positive outcomes.

Vitamin C has many physiologic benefits. In sepsis and other acute disease processes, it decreases endothelial barrier permeability. This improves tissue edema and may secondary decrease organ dysfunction. There is also improvement in micro vascular function via prevention intracellular adhesion molecule expression which reduces plugging in micro vessel and microcirculatory flow impairment. In addition, there is some possible bacterial static activity of vitamin C as it influences macrophage activity and bacterial growth [1,4]. Finally, vitamin C increases endogenous synthesis of norepinephrine and vasopressin by serving as a cofactor of dopamine b-hydroxylase and tyrosine hydroxylase in the synthesis of norepinephrine [5]. Ascorbate is a cofactor for the copper-containing enzyme peptidylglycine α-amidating monooxygenase (PAM) that is required for the endogenous synthesis of vasopressin [6].

The physiologic importance of vitamin C has been shown to translate into clinical benefits as well. Several studies have now shown improved clinical benefits associated with vitamin C in critically ill patients. In a retrospective before-after clinical study, septic patients treated with combination of intravenous vitamin C, hydrocortisone, and thiamine demonstrated lower mortality when compared with placebo (8.5% vs 40.4%, $p<0.001$) [7]. In a prospective randomized controlled study, 100 patients with septic shock received either placebo or intravenous 1.5 gm vitamin C every 6 hours in the first 24 hours after admission until ICU discharge plus conventional sepsis treatment. The mean number of days on vasopressor was significantly less in vitamin C group than in control group (2.30 vs 6.50 days, $p=0.001$). The vitamin C group also has shorter intensive care unit stay compared to the control group (10 vs 14.1 days $p=0.04$) [8]. In another study, patients with septic shock were randomized to receive either vitamin C 25mg/kg intravenous every 6 hours or placebo for 72 hours. The vitamin C group in this study demonstrated decrease in 28 days mortality (14.28% vs. 64.28%, $p = 0.009$) [9].

Beyond the previously mentioned impact of vitamin C in critically ill patients, there is a growing body of evidence showing improved clinical outcomes with vitamin C in other patient populations. A retrospective review in Japan shows that burn injury patients with more than 20% total body surface area (TBSA) who received vitamin C at 66 mg/kg/hr. has less fluid requirements than the placebo group (5.3 ± 1ml/kg/ %TBSA vs 7.1 ± 1 ml/kg/ %TBSA, $p<0.05$) [10]. In another

prospective randomized controlled study, patients with more than 30% TBSA burn injury who received vitamin C (66mg/kg/hr.) required less fluid than placebo group (3 ± 1.7ml/kg/%TBSA vs 5.5 ± 3.1ml/kg/ %TBSA, p <0.01) [11].

After cardiac surgery, a massive depletion of vitamin C has been observed [4]. The data supporting the use of vitamin C for prevention of a trial fibrillation however is conflicting. Patients who underwent coronary artery bypass grafting who received oral vitamin C the night before and 5 days after surgery, had a lower incidence of postoperative a trial fibrillation [12,13]. However, a subsequent larger trial has shown no difference in incidence of a trial fibrillation although it did show a decrease in mechanical ventilation favoring vitamin C use [14]. There is likely benefit for vitamin C in preventing a trial fibrillation post cardiac surgery but timing, route and dose of vitamin C, and in the combination of other antioxidants has yet to be determined.

Although frequently thought of as potentially nephrotoxic, vitamin C has been shown to be potentially renal protective. Reactive oxygen species (ROS)-induced oxidative stress and renal vasoconstriction have been implicated in the etiology of contrast induced nephropathy (CIN) [15]. In patients undergoing coronary angiography and/or intervention, oral vitamin C before and after the procedure resulted in lower incidence of CIN when compared with placebo (9% vs 20%, p=0.02) [16]. A recent systematic review that included 1536 patients showed that patients receiving vitamin C had 33% less risk of CIN compared with placebo or an alternate pharmacological treatment (RR: 0.672, p = 0.034) [15].

Clearly vitamin C offers both clinical and physiological improvements for critically ill patient populations. Vitamin C is a common supplement sold over the counter and taken by many patients at various doses. There is little harm associated with vitamin C and no major adverse events in the existing body of evidence. Patients should therefore receive the potential benefit of vitamin C while we await a larger clinical trial.

CON

There are multiple studies often cited favoring vitamin C in critical illness and used as evidence to support the current widespread use of vitamin C. However, at present the argument to use vitamin C in critically ill patients is remindful of the famous Mark Twain quote; lies, damned lies, and statistics. Simply put a valid statistically based argument to treat septic or critically ill patients with vitamins C is lacking. Although, the impact of vitamin C in these patient populations warrants study in a large multi-center trial, this should be complete prior to it becoming standard therapy.

Linus Pauling would be proud, as it has now been claimed that vitamin C has successfully treated patients with trauma, burns, tetanus, coronary artery bypass surgery, and sepsis [17]. However, this evidence if evaluated in detail is less convincing that it is successful treatment vs. hypothesis generating theories. Vitamin C certainly has been studied in the above-mentioned populations, but in small studies and typically in combination with other anti-oxidants leaving in question which intervention provided the most benefit. In one of the largest studies of trauma patients, it was combined with vitamin E and selenium in high doses. In this study patients in the intervention group showed an improvement in mortality, however the study is a retrospective cohort study and involves additional interventions other than vitamin C alone [18].

A second study of surgical patients by Nathens et al. [19] enrolled 595 patients in a prospective non-blinded trial with an intervention that included vitamin C and E together. The composite primary endpoint for this trial was ARDS and/or pneumonia. The study found no difference between the two groups as the relative risk of pulmonary morbidity was 0.81 (95% CI 0.60-1.1) in patients receiving antioxidants [19]. A randomized double blinded study to evaluate the effect of high dose vitamin C on vasopressor drug requirements in septic shock was published in 2016. However, this study is small and underpowered to accurately reflect any true benefit in the primary outcome. The study does show a decrease in the overall dose of vasopressor favoring the group receiving vitamin C. The total enrollment for this study was only 28 patients (14 in each study group) which are inadequate for statistical validity [9]. This and the other previously mentioned studies are interesting for hypothesis generating, but cannot be considered adequate for clinical decision making or evidence of successful treatment with vitamin C in surgical patients.

The studies of vitamin C in sepsis have similar flaws as the surgical studies. One study by Fowler et al. enrolled 24 patients of which only 16 patients received vitamin C. This study is a phase one trial for evaluation of the safety profile, however it is often cited as evidence that vitamin C reduces Sequential Organ Failure Assessment (SOFA) scores in patients with sepsis [20]. The enrollment for the study is low and therefore cannot support any statistically valid conclusion regarding the impact of vitamin C in sepsis compared to the control group. It is inaccurate to state vitamins C lowers SOFA scores in patients with sepsis based on this clinical trial.

Finally, the most recent trial by Marik et al. [7] shows possible benefits for vitamin C in patients with sepsis but it is not a randomized trial with adequate statistical power to justify a large-scale change in medical practice. The study, as stated by the authors, has limitations. It is a single center, small sample size with non concurrent control subjects [7]. There is statistical bias in this study (based on its design alone) and this bias may or may not favor the treatment group. Regardless, this should give the clinician pause when implementing changes to medical practice.

The Marik study like many other clinical trials do not show any potential harms in providing vitamin C to critically ill patients. The study authors justify broad scale use of vitamin

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C prior to a large clinical trial given this lack of evidence of harm. However, the overall total number of patients to receive vitamin C in an objective trial remains relatively small. Dr. Walter and Dr. Singer point out in a letter to the Editor of Chest that it cannot be assumed that vitamin C is safe for all critically ill patients [21]. They point to glutamine (a nutrition supplement) as an example of why we should proceed with caution.

Glutamine, an amino acid, once held the lime light as vitamin C does now as an anti-oxidant and immune modulator that could improve patient outcomes in critical illness. Many of the early clinical trials demonstrated glutamine supplementation appeared to reduce infections, ICU and hospital length of stay, and mortality [22]. These studies consisted mainly of single-center small randomized control trials which were likely underpowered to show statistically valid outcome data and detect potentially adverse events associated with glutamine. Many clinicians advocated for and used glutamine as therapy in critically ill patients. However, when studied in a large multi-center (REDOX) trial published in 2013, glutamine was shown to have no benefit and potential for harm in patients with sepsis [23].

It would be unfair to assume vitamin C will fail in the same way glutamine did in the large multi-center trial. However, it is also foolish to repeat the past and assume that small underpowered and non-randomized trials with promising data are unflawed. Vitamin C should be studied in a multi-center trial, but current use in medical practice is without good clinical evidence and outside the standard of care.

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