Evidence-Based Case Report

The Benefits of High-Dose Vitamin C in Patients with Sepsis

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Abstract

In sepsis, there is an increase in oxidative stress which plays important role in further physiological derangement. Due to its potent antioxidant effect, vitamin C has been proposed as a potential adjunct treatment in patients with sepsis. This study aims to evaluate the benefits of vitamin C administration in patients with sepsis. A systematic search was conducted using electronic databases PubMed, Scopus, ProQuest, and Cochrane with keywords combination of vitamin C/ascorbic acid and sepsis/septic. The limits of the search included English language, human subjects, and adults. To limit the confounding effect, only studies with vitamin C monotherapy were considered for inclusion. Seven relevant studies comprising five clinical trials and two retrospective studies were included in this paper for critical appraisal. Most studies found some clinical benefits with the use of vitamin C in patients with sepsis compared to placebo, such as a reduction in SOFA score and mortality. However, these favourable outcomes were not consistent in all studies. In conclusion, vitamin C is a promising adjunct treatment option in patients with sepsis, however further large, optimized multicenter trials are needed to definitively confirm its benefits.
Keywords: *vitamin C, ascorbic acid, sepsis, septic shock.*

Manfaat Vitamin C Dosis Tinggi untuk Pasien Sepsis

Abstrak

Kondisi sepsis menyebabkan peningkatan stres oksidatif yang berperan penting dalam menyebabkan gangguan fisiologis lebih lanjut. Karena memiliki efek antioksidan yang kuat, vitamin C telah diusulkan sebagai terapi adjuvan yang menjanjikan pada pasien sepsis. Penelitian ini bertujuan untuk mengevaluasi manfaat pemberian vitamin C pada pasien sepsis. Pencarian sistematis dilakukan menggunakan database elektronik PubMed, Scopus, ProQuest, dan Cochrane dengan kombinasi kata kunci vitamin C/asam askorbat dan sepsis/ septik. Batas pencarian yaitu bahasa Inggris, subjek manusia, dan usia dewasa. Untuk membatasi efek perancu, hanya studi yang menggunakan monoterapi vitamin C yang dipertimbangkan untuk dimasukkan. Tujuh studi relevan yang terdiri dari lima uji klinis dan dua studi retrospektif dimasukkan dalam tulisan ini untuk telaah kritis. Sebagian besar studi mendapatkan manfaat klinis penggunaan vitamin C pada pasien sepsis dibandingkan dengan plasebo, misalnya penurunan skor SOFA dan angka mortalitas, namun hasil positif ini tidak konsisten dalam semua penelitian. Sebagai kesimpulan, vitamin C adalah pilihan terapi adjuvan yang menjanjikan pada pasien sepsis, namun butuh penelitian multisenter yang lebih besar dan optimal untuk memastikan manfaatnya secara definitif.
Kata kunci: *vitamin C, asam askorbat, sepsis, syok sepsis.*

Introduction

Sepsis is a severe and highly lethal condition, globally affecting more than 30 million people per year, and causing 5-6 million deaths.[1] Despite major progress in diagnostic and therapeutic modalities, mortality from sepsis remains as high as 30-80%, depending on the severity.[2] Furthermore, despite numerous clinical trials over the last three decades, many novel potential drugs and interventions were unsuccessful in curbing organ failure and improving the survival of patients with sepsis and even causing harm instead.[3] Antibiotics, source control, and preservation of hemodynamic stability through fluid administration and vasopressors continue to be the hallmarks of current sepsis therapy.[4] Unfortunately, however, death or disability frequently ensues in spite of these supportive treatments, thus novel, targeted adjuvant treatments are required in septic patients.

It is noteworthy that antioxidant supplementation is not in the current recommendations of sepsis therapy, even though oxidative stress is elevated in sepsis. During sepsis pathogenesis, reactive nitrogen species and reactive oxygen species, two major culprits of oxidative stress, are highly produced in the microvascular endothelial cells.[5] This oxidative stress facilitates the systemic inflammatory response syndrome that leads to various typical pathological processes of sepsis, such as injury of the cellular membranes and inter-cellular junctions. Such damage may eventually disturb the microcirculation, underlying the clinical signs and symptoms characteristic of sepsis such as hypotension and multiorgan dysfunction.

One of our cells responses to raised oxidative stress in sepsis is by increasing the metabolic utilization of vitamin C, our potent and key cellular antioxidant, which may cause acute deficiency of vitamin C. Indeed, critically ill septic patients often have extremely low or even undetectable serum levels of vitamin C,[6] which is associated with an increased risk of developing multiorgan failure.[7] Therefore, vitamin C has been proposed as a potential adjunct therapeutic agent.

Many preclinical studies have reported the benefits of vitamin C and its associated effects against sepsis. The detailed mechanisms are complex but concise, vitamin C directly scavenges elevated free radicals within the cells, prevents the production of free radicals, restores other antioxidants, and reduces endothelial permeability and cellular apoptosis. It plays role in endothelial cell proliferation, epithelial barrier function, and smooth muscle-mediated vasodilation, all of which are pathophysiologically changed in sepsis. Vitamin C also improves arteriolar responsiveness to vasopressors and increases the endogenous synthesis of norepinephrine and vasopressin as a cofactor, which is beneficial in septic shock. Moreover, vitamin C has bacteriostatic activity and can increase microvascular blood flow.[8]

Therefore, the administration of vitamin C to patients with sepsis may theoretically lead to an earlier resolution of septic shock, prevent further development of multiorgan failure, and decrease mortality. In light of this, recently there is an increased interest in clinical studies investigating the benefits of vitamin C in patients with sepsis, arguably started by the retrospective before-after study by Marik et al,[9] in 2018 which demonstrated that administration of high-dose vitamin C in combination with hydrocortisone and thiamine to patients with severe sepsis or septic shock significantly caused a remarkable reduction of mortality compared to matched controls (8.5% vs 40.4%).[9] The presence of three simultaneous agents, however, confounded the potential effects of vitamin C and limit the generalizability of the results. Unfortunately, however, clinical studies investigating the effect of vitamin C on its own are scarce. Therefore, the purpose of this study is to evaluate the potential benefits of vitamin C monotherapy in patients with sepsis or septic shock.

Clinical Case

A 31-year-old man was admitted to the hospital with a chief complaint of low food intake since one week before admission. He also felt weak and had a low appetite. The malnourished patient had a history of colon cancer in the past five months, first detected due to complaints of recurrent severe abdominal pain and anorexia. At the time of diagnosis, the cancer had been in an advanced stage where it had metastasized to the liver and obstructed the left ureter. During the hospital care, however, the patient had high-risk hospital-acquired pneumonia and his clinical condition progressively deteriorated into sepsis and subsequently septic shock. The patient's family chose to do not to resuscitate him and hence was not admitted to the intensive care unit. Despite maximum efforts with judicious fluid and vasopressor administration, definitive antibiotic therapy, source control, and optimal nutritional support, the patient did not improve and finally died after almost a month of hospitalization.

Formulation of the Problems
Clinical Question

Is there any clinical benefit of administering high-dose vitamin C to adult patients with sepsis?

Methods

PICOS in this study was as following:

- Population: adult patients with sepsis
  Comorbidities were not limited since it was expected that sepsis studies would involve patients with various, multiple comorbidities, i.e. such heterogeneity which was an inherent limitation of these studies. The patient in the clinical case above had advanced-stage cancer as comorbidity. However, the effect of high-dose vitamin C on advanced-stage cancer itself is still contentious,[10] thus this study did not specifically limit the search to septic patients with malignancy.
- Intervention: high-dose vitamin C
  High-dose vitamin C alone was used as the intervention to limit the confounding effect of combination therapy. Standard treatment in addition to vitamin C was expected to be different between studies, which was another limitation of sepsis studies.
- Comparison: placebo
  Placebo was chosen as the comparison to help minimize heterogeneity.
- Outcome: improvement in biomarker or clinical outcomes
  Biomarkers such as inflammatory markers and clinical outcomes such as mortality were the main interests in this study. The safety of the intervention was also evaluated.
- Study: clinical studies
  Besides randomized controlled trials, cohort studies were also included to expand the scope of knowledge. Only original primary data were included in this paper, thus meta-analysis and systematic review were not included, but they were read to further find relevant studies which may not be found on an initial search from databases.

Searching Strategy

Comprehensive computer-based searching of literature was conducted using the electronic database PubMed, Scopus, ProQuest, and Cochrane on September 4th, 2021. The search used Boolean combination (AND, OR) with keywords as follows: vitamin C/ascorbic acid and sepsis/septic. The limits of the search included English language, human subjects, and adults. Only studies in which the treatment group received vitamin C alone and the control group received a placebo were included in this paper. Title and abstract were manually screened to ensure all relevant studies were identified, and references from relevant studies were manually assessed to identify additional relevant studies. Finally, selected studies were appraised by the authors (MM, NH, SM) using the Oxford model of evidence-based medicine and CLARITY risk of bias tool.

Results

Literature search using the aforementioned keywords and limitations across four databases initially showed a total of 2,029 studies, and 1,897 studies after filtering for duplicate results (Figure 1). Only 348 studies were considered relevant based on their title and abstract. After reading the full text, finally, seven studies were included in this paper for critical appraisal, i.e. studies by Ahn et al,[23] Aisa-Alvarez et al,[17] Ferron-Celma et al,[18] Fowler et al,[12,14] Natarajan et al,[20] and Zabet et al.[13]

Out of seven studies, six studies were randomized clinical trials and one study was a retrospective cohort study. Studies included septic patients ages ranging from 18-95 years. Most studies had a small number of samples, except the CITRIS-ALI trial by Fowler et al[12,14] which involved 167 subjects. The vitamin C dose varied from 50 mg/kg/d to 200 mg/kg/d, administered for 3-19 days, compared to placebo. Five studies mainly assessed clinical outcomes such as mortality and ICU length of stay, whereas two studies primarily assessed biomarkers of sepsis. The description of each study is summarized in Table 1.

Critical Appraisal

Relevant studies were critically appraised using Oxford's standardized validity, importance, and applicability assessments for therapy studies (Table 2-4). Indicators of importance are mainly represented by 28-day mortality, changes in SOFA score, and ICU length of stay, if applicable (Table 3). Additionally, results of primary outcomes from each study were also accounted for. Finally, CLARITY risk of bias tool was used as presented in Table 5 & 6.

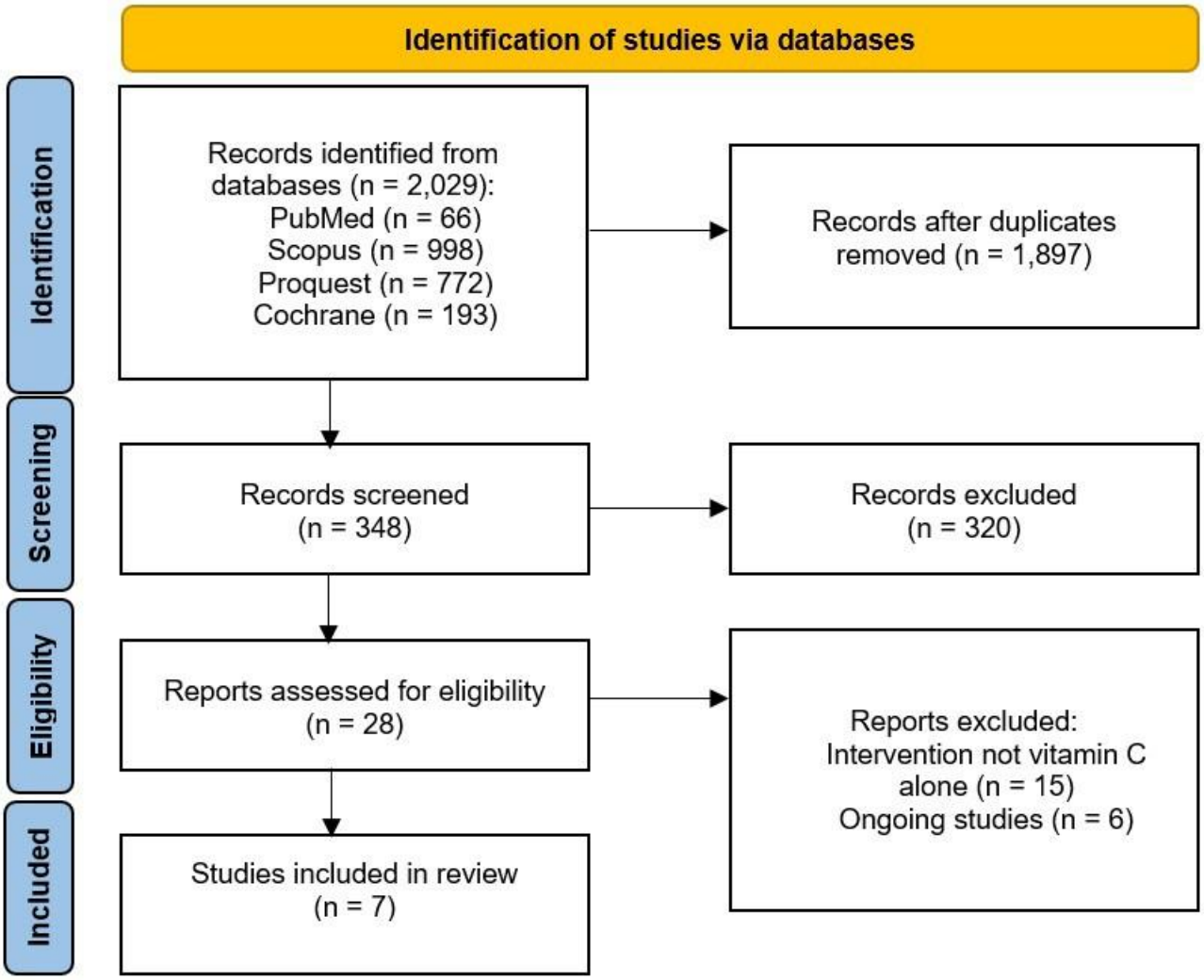

Figure 1. Flowchart of The Searching Methods

Discussion

The basis of vitamin C administration in sepsis is strong given the fact that there is increased oxidative stress in sepsis, causing increased demand of antioxidants which often leads to depletion of vitamin C, our main cellular antioxidant. Furthermore, vitamin C has capacities as a neuroprotector, immunomodulator, and cofactor for the synthesis of vasopressors, and it can also restore other antioxidants and reduce endothelial permeability, all of which are beneficial in sepsis.[11] Given its high potential, it is interesting that most studies included in this paper managed to show some benefits of vitamin C in patients with sepsis, although the results were not consistent across all studies. For instance, out of seven studies in this paper, four studies found significant improvement in biomarker levels of sepsis with vitamin C, but only two studies found significantly reduced 28-day mortality and only one study had the ICU length of stay reduced markedly by vitamin C.

The phase I randomized trial by Fowler et al[12] demonstrated the benefits of high-dose vitamin C in ICU patients with severe sepsis where it significantly reduced the daily SOFA score by over 96 h compared to placebo. Furthermore, vitamin C also significantly attenuated circulating injury biomarker levels, i.e. CRP & procalcitonin, while being well tolerated. However, this study was not powered to assess mortality, thus it could not demonstrate any significant effect on 28-day mortality.

Table 1. Description of The Included Studies

Description	Ahn et al[23]	Aisa-Alvarez et al[17]	Ferron-Celma et al[18]	Fowler et al[12]	Fowler et al[14]	Natarajan et al[20]	Zabet et al[13]
Methods	Retrospective cohort study in a center in South Korea in 2017	Triple-blind, randomized trial in 2 centers in Mexico from 2018-2019	Double-blind, randomized trial in a center in Spain	Double-blind, randomized trial in a center in USA	Double-blind, randomized trial in 7 centers in USA from 2014-2017	Retrospective study of a double-blind, randomized trial in a center in USA	Double-blind, randomized trial in a center in Iran from 2014-2016
Population	n = 75 Inclusion criteria: adults with severe sepsis or septic shock and required mechanical ventilation	n = 39 Inclusion criteria: adults with septic shock	n = 20 Inclusion criteria: septic patients undergoing abdominal surgery with postoperative mortality risk >30%	n = 24 Inclusion criteria: adults with severe sepsis	n = 167 Inclusion criteria: adults with sepsis & ARDS & mechanical ventilation	n = 24 Inclusion criteria: adults with severe sepsis	n = 28 Inclusion criteria: critically ill surgical adult patients with septic shock & needed vasopressor
Intervention	Vitamin C 2 g q8 h IV for a median of 9 d (IQR 5-19 d)	Vitamin C 1 g tablet q6h for 5 d	Vitamin C 450 mg/d IV in 3 divided doses for 6 d	Vitamin C 50 mg/kg/d or 200 mg/kg/d IV, divided q6 h for 96 h	Vitamin C 50 mg/kg q6h for 96 h	Vitamin C 50 mg/kg/d or 200 mg/kg/d IV, divided every 6 h for 96 h	Vitamin C 25 mg/kg IV q6h for 72 h
Comparison	Placebo	Placebo	Placebo	Placebo	Placebo	Placebo	Placebo
Outcomes	Primary: hospital mortality Secondary: ICU mortality, 90-day mortality, time to shock reversal, doses of vasopressors, duration of mechanical ventilation, changes in SOFA scores, ICU & hospital lengths of stay	Primary: SOFA score, oxidative stress markers, CRP, procalcitonin Secondary: 28-day mortality, ventilator-free days, ICU & hospital-free days	Neutrophil apoptosis markers (Fas receptor expression, level of caspase-3, poly (ADP-ribose) polymerase (PARP), Bcl-2)	Primary: vitamin C safety & tolerability Secondary: days on vasopressor, ventilator-free days, ICU length of stay, 28-d mortality	Primary: change in SOFA score, CRP, thrombomodulin Secondary: all-cause mortality at day 28, ventilator & ICU-free days to day 28, hospital-free days at day 60	Novel biomarkers of sepsis: circulating cell-free DNA, mitochondrial DNA, endogenous antimicrobial proteins (alpha-4-defensin and bactericidal permeability interacting protein), the red cell distribution width	Primary: vasopressor dose and duration Secondary: ICU length of stay & 28-day mortality
Notes	Not randomized/ blinded. Not stated: participants' race, funding source	Not stated: participants' race	Not stated: study duration, exclusion criteria, participants' race, the dropout rate	Not stated: study duration, participants' race, mean age, dropout rate, funding source	Not stated: funding source	Not stated: study duration, participants' race, mean age, dropout rate, funding source	No financial support and sponsorship. Not stated: participants' race, the dropout rate

Table 2. Appraisal of Validity

Description	Ahn et al[23]	Aisa-Alvarez et al[17]	Ferron-Celma et al[18]	Fowler et al[12]	Fowler et al[14]	Natarajan et al[20]	Zabet et al[13]
Was the assignment of patients to treatments randomized?	✗	✓	✓	✓	✓	✓	✓
Were the groups similar at the start of the trial?	✓	✓	✓	✓	✓	✓	✗
Aside from the allocated treatment, were groups treated equally?	✓	✓	✓	✓	✓	✓	✓
Were all patients who entered the trial accounted for? – and were they analyzed in the groups to which they were randomized?	✓	✓	✓	✓	✓	✓	✓
Were measures objective or were the patients and clinicians kept “blind” to which treatment was being received?	✗	✓	✓	✓	✓	✓	✓

Table 3. Appraisal of importance

Description	Ahn et al[23]	Aisa-Alvarez et al[17]	Ferron-Celma et al[18]	Fowler et al[12]	Fowler et al[14]	Natarajan et al[20]	Zabet et al[13]
28-day mortality	34% (vit C)§ 20% (control)	Value not stated but no significant difference	-	38.1% (low-dose vit C)§ 50.6% (high-dose vit C)§ 62.5% (control)	29.8% (vit C)* 46.3% (control)	38.1% (low-dose vit C)§ 50.6% (high-dose vit C)§ 62.5% (control)	14.28% (vit C)† 64.28% (control)
Mean changes in SOFA score	-1.4 (vit C)§ -1.4 (control)	-1.94 (vit C)‡ Control not stated	-	-0.02 (low-dose vit C)* -0.04 (high-dose vit C)† 0.003 (control)	-3 (vit C)§ -3.5 (control)	-0.02 (low-dose vit C)* -0.04 (high-dose vit C)† 0.003 (control)	-
Mean ICU length of stay (days)	10 (vit C)§ 11 (control)	Value not stated but no significant difference	-	8.1 (low-dose vit C)§ 9.1 (high-dose vit C)§ 11 (control)	17.3 (vit C)* 20.3 (control)	8.1 (low-dose vit C)§ 9.1 (high-dose vit C)§ 11 (control)	21.45 (vit C)§ 20.5 (control)
Other primary outcomes of individual study	-	Significantly lower nitrate/nitrite ratio and C-reactive protein in vit C group.	Significant antiapoptotic effects in vit C group.	No patient in both vit C groups had any treatment-related adverse event.	No significant effect of vit C to level of plasma C-reactive protein and thrombomodulin.	Significant improvement in novel sepsis biomarkers in vit C group.	Significantly lower norepinephrine dose and duration in vit C group.

*p <0.05 vs control, †p <0.01 vs control, ‡p <0.001, §p >0.05 (non-significant), CI: confidence interval, IQR: interquartile range, PARP: poly (ADP-ribose) polymerase, RDW: red cell distribution width, SD: standard deviation

Table 4. Appraisal of applicability

Description	Ahn et al[23]	Aisa-Alvarez et al[17]	Ferron-Celma et al[18]	Fowler et al[12]	Fowler et al[14]	Natarajan et al[20]	Zabet et al[13]
Is my patient so different to those in the study that the results cannot apply?	✗	✗	✗	✗	✗	✗	✗
Is the treatment feasible in my setting?	✓	✓	✓	✓	✓	✓	✓
Will the potential benefits of treatment outweigh the potential harms of treatment for my patient?	✓	✓	✓	✓	✓	✓	✓

Table 5. Risk of Bias Assessment in Cohort Study

Description	Ahn et al[23]
Was selection of exposed and non-exposed cohorts drawn from the same population?	*
Can we be confident in the assessment of exposure?	**
Can we be confident that the outcome of interest was not present at start of study?	**
Did the study match exposed and unexposed for all variables that are associated with the outcome of interest or did the statistical analysis adjust for these prognostic variables?	**
Can we be confident in the assessment of the presence or absence of prognostic factors?	**
Can we be confident in the assessment of outcome?	***
Was the follow up of cohorts adequate?	*
Were co-interventions similar between groups?	**

*Definitely yes (low risk of bias), **probably yes, ***probably no, ****Definitely no (high risk of bias)

Table 6. Risk of Bias Assessment in Randomized Controlled Trials

Description	Ahn et al,[23]	Aisa-Alvarez et al,[17]	Ferron-Celma et al,[18]	Fowler et al,[12]	Fowler et al,[14]	Natarajan et al,[20]
Was the allocation sequence adequately generated?	*	*	*	**	*	**
Was the allocation adequately concealed?	*	*	*	**	*	**
Blinding: Was knowledge of the allocated interventions adequately prevented?	*	**	**	**	**	**
Were patients blinded?	*	**	*	* *	*	*
Were healthcare providers blinded?	*	**	**	* *	*	*
Were data collectors blinded?	*	**	**	** **	**	**
Were outcome assessors blinded?	*	**	**	** **	**	**
Were data analysts blinded?	**	**	**	** **	**	**
Was loss to follow-up (missing outcome data) infrequent?	*	**	*	* *	*	*
Are reports of the study free of selective outcome reporting?	**	**	**	** **	**	*

*Definitely yes (low risk of bias), **probably yes, ***probably no, ****Definitely no (high risk of bias)

Zabet et al[13] also found that vitamin C had benefits on vasopressor requirements in surgical ICU patients with septic shock. Patients who received vitamin C showed a significant reduction in duration and dose of vasopressor. Furthermore, the vitamin C group had a significant decrease in 28-day mortality compared to the control (14.28% vs 64.28%). These beneficial effects, however, could be attributed to the lower baseline severity in the treatment group. Moreover, the small number of study subjects without statistical sample size calculation might affect the results.

Fowler et al[14] followed their trial with the largest multicenter trial of vitamin C in patients with sepsis to date, i.e. the CITRIS-ALI trial which involved 167 ICU patients with sepsis and ARDS on mechanical ventilation. The Vitamin C group, however, failed to show any significant improvement in primary outcomes that evaluated organ dysfunction and markers of inflammation and vascular injury. Furthermore, only 3 out of 46 secondary outcomes showed significant differences in favor of vitamin C, i.e. improvement in 28-day all-cause mortality, increased ICU-free days, and increased hospital-free days. The marked improvement in mortality in the treatment group (29.8% vs. 46.3%), however, was the highlight of this study. They suggested that the reduction in mortality was not reflected in the improvement of most other parameters due to the ameliorating effects of vitamin C on other sepsis-induced biological markers that were not analyzed in their study. It is possible that the positive result in this study was due to early administration of vitamin C (within 6 h) and a far higher dose of vitamin C compared to other studies (50 mg/kg every 6 h for 96 h). However, notably, 66% of patients in their study received corticosteroids, which might confound the results as it has been shown that corticosteroids work synergistically with vitamin C, but not on their own.[15]

Previously it was thought that intravenous dosing of vitamin C was necessary since high-level plasma concentration of vitamin C could not be achieved by enteral intake.[16] Interestingly, a recent trial by Aisa-Alvarez et al[17] does find that the oral or enteral route of 1 g vitamin C alone every 6 h for 5 d manages to significantly restore plasma concentration of vitamin C in septic shock patients, leading to a significant reduction of SOFA score, CRP, and nitrate/nitrite ratio.[17] They suggest that these favourable results could be attributed to earlier administration of vitamin C (median time 5 h) compared to other studies. Outcomes such as intrahospital mortality, however, are not reduced due to the underpowered sample size for such outcomes.

Other studies tried to examine the effects of vitamin C on relatively uncommon sepsis-associated markers, such as the trial by Ferron-Celma et al[18] which investigated the effect of vitamin C on neutrophil apoptosis of septic abdominal surgery patients. During sepsis, widespread and dysregulated apoptosis of leukocytes may lead to multiorgan dysfunction.[19] Vitamin C seemed to exert an antiapoptotic effect on peripheral blood neutrophils as shown by significantly reduced caspase-3 and poly (ADP-ribose) polymerase (PARP) levels, and significantly increased Bcl-2, possibly mediated by its potent oxidative stress-scavenging capacity. Unfortunately, clinical outcomes such as postsurgical complications and mortality were not assessed in this study, which could reflect the antiapoptotic benefits of vitamin C.

Similarly, using the patient data from the Fowler et al[12] phase I trial, Natarajan et al[20] evaluated vitamin C's effect on novel biomarkers associated with sepsis-related mortality, i.e. circulating cell-free DNA (cfDNA), mitochondrial DNA (mtDNA), endogenous antimicrobial proteins (alpha-4-defensin and bactericidal permeability interacting protein), and the red cell distribution width (RDW).[20] Unfortunately, both cfDNA and mtDNA were not significantly reduced with vitamin C. They did find that vitamin C significantly reduced RDW and increased levels of host defensins, which might be beneficial in sepsis. Increased RDW is associated with higher severity and mortality in sepsis,[21] while increased defensins indicate augmented host antibacterial defence.[22]

In contrast to other studies in this paper, a retrospective cohort study by Ahn et al[23] found that vitamin C did not exert any benefit on ICU patients with severe sepsis or septic shock.[23] The primary outcome of intrahospital mortality and all secondary outcomes such as changes in SOFA scores and hospital length of stay were not improved. They suggested three possible reasons for these negative results, i.e. (1) the patients in this study were in too severe condition for the vitamin C to alter the course of sepsis, (2) the timing of vitamin C was relatively late (median time 16 h), and (3) vitamin C on its own was inadequate to amend the harmful processes of sepsis, suggesting the need of combination therapy. However, it is notable that this study was neither blinded nor randomized which might cause bias.

Other clinical studies have attempted to investigate the effect of vitamin C in combination with other therapy in patients with sepsis. However, it was not until 2018 that huge interest in vitamin C cocktail therapy emerged when a retrospective before-after study by Marik et al[9] found that vitamin C in combination with hydrocortisone and thiamine caused an astounding 31.9% absolute risk reduction in mortality of patients with severe sepsis or septic shock, suggesting that multiple and overlapping effects of these medications synergistically alter the natural course of sepsis, which could not be attained with each drug alone.[9] The study, however, is limited by single centre design, before-and-after non-blinding study design, and small sample size.

Regardless, several studies have tried to further investigate the benefits of such combination therapy, albeit with mixed results,[24-30] most likely due to the inherent heterogeneous nature of sepsis studies. Some of these studies are included in a recent meta-analysis by Scholz et al. which concludes that pooled analysis indicates no significant mortality reduction in patients treated with vitamin C, either alone or in combination.[31] Several large multi-centre trials are underway to confirm these results, which hopefully will provide definitive evidence.

None of the included studies in this paper reported major adverse effects of vitamin C therapy, although using very high doses. Indeed, vitamin C is generally safe for most patients. Besides the increased risk of hemolysis in patients with glucose-6-phosphate dehydrogenase deficiency and paroxysmal nocturnal hemoglobinuria,[32,33] one of its known complications is dose-dependent calcium oxalate nephropathy.[34] However, patients with sepsis most likely only necessitate high-dose vitamin C for a few days until source control and antibiotics have cleared the pathogens, thus such a short course of therapy probably would not be a major risk for oxalate stone formation, except in patients with reduced kidney function. There is a valid concern, however, that the accuracy of point-of-care blood glucose measurements may be reduced with high-dose vitamin C since the molecular structures of vitamin C and glucose are rather identical,[35] thus such measurements should be approached with caution.

All in all, the effects of vitamin C in patients with sepsis are promising but not without caveats. Although most studies in this paper favor vitamin C and found no major safety issue, its benefits, however, are not consistent across many important clinical outcomes. Such a fact is unsurprising since sepsis is a heterogenous syndrome with an equally heterogenous patient population, which might contribute to the heterogeneities of results across studies. Furthermore, the onset and duration of the intervention varied, and there were non-standardized co-interventions and a lack of large multicenter trials. Further studies are needed to address these issues, as currently the evidence of vitamin C, whether alone or in combination with other agents, are insufficient to introduce changes into clinical practice, limiting its applicability. Hopefully, however, the potential benefits and overall safety of this highly accessible agent would warrant a place in the treatment of such an extremely lethal condition with very limited alternative therapeutic options.

Conclusion

Sepsis remains a serious and life-threatening condition with high morbidity and mortality. It is marked by elevated oxidative stress, dysregulated inflammation, and hemodynamic instability. Vitamin C as a potent antioxidant has been associated with the alleviation of these detrimental processes. Clinical findings are promising regarding its effectiveness as an adjunct treatment agent in patients with sepsis as most of the included studies showed some favorable results with vitamin C (level of evidence 1 and 3), such as reduction in mortality and SOFA score. However, these findings are not consistent across all studies, thus further research is required to prove the value of vitamin C in sepsis treatment.

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