Effect of vitamin C in critically ill patients with sepsis and septic shock: A meta-analysis

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Abstract
The objective of this study was to investigate the efficacy of vitamin C in patients experiencing sepsis and septic shock. The PubMed, Embase and Cochrane Library databases were searched for randomized controlled trials (RCTs) about vitamin C treatments for critically ill patients suffering from sepsis and septic shock from inception until December 31, 2019. The primary outcome was mortality, and the secondary outcomes were the ICU length of stay and the dose of vasopressors. A meta-analysis of nine RCTs with a total of 584 patients (301 in the intervention group and 283 in the control group) was conducted. There were significant differences between the vitamin C group and the control group in 28-day mortality (fixed effects OR = 0.60 95% CI [0.42, 0.85], p = 0.004) and in the dose of vasopressors (SMD = −0.88 95% CI [−1.48, −0.29], p = 0.003); however, the ICU length of stay was the same between the two groups (SMD = −0.33 95% CI [−0.87, 0.20], p = 0.23). This meta-analysis demonstrated that the use of vitamin C (compared with placebo) led to a reduction in ICU mortality and a reduction in the dose of vasopressors in patients with septic shock. However, the ICU length of stay was not significantly different between the two groups. Therefore, multicentre and high-quality RCTs are needed to further clarify the safety and effectiveness of vitamin C among patients with sepsis and septic shock.

Keywords
Sepsis, septic shock, critically ill patients, vitamin C, meta-analysis

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Background

The Surviving Sepsis Campaign 2016 provided international guidelines that defined sepsis as a life-threatening organ dysfunction syndrome caused by infections.\(^1\) Sepsis can lead to numerous disorders. Previous studies\(^2\) have shown that the prevalence of sepsis in critically ill patients was 37.3%, of which 9.2% developed septic shock, and the mortality rate of sepsis was 42.7%. Therefore, sepsis is one of the most severe complications among critically ill patients and is a significant public health problem. Currently, treating sepsis mainly entails controlling the source of the infection, administering antibiotic drugs, performing fluid resuscitation, administering vasoactive drugs, and other supportive treatments. Although a large number of therapeutics have been explored and applied, the mortality of sepsis has not been significantly reduced; thus, seeking new adjuvant therapies to improve the prognosis of patients with sepsis has become crucial.\(^3\) Existing research evidence shows that vitamin C supplementation can reduce oxidative stress injury and organ dysfunction in patients with sepsis/septic shock, improve microcirculation, and reduce a patient’s dependence on vasoactive drugs. Vitamin C is cheap and effective, and its application in critically ill patients is very promising, leading to new ideas in clinical research on the treatment of critically ill patients with vitamin C. Although preliminary evidence supports the use of vitamin C in patients with sepsis/septic shock, the appropriate timing of administration, the mode of administration, and its interaction with other antioxidants are still unknown.

Vitamin C,\(^4\) also known as ascorbic acid, is an essential antioxidant and enzyme cofactor involved in many crucial chemical reactions. In sepsis, the oxidative stress response is exceptionally enhanced, resulting in a large number of reactive oxygen species, extensive endothelial cells, and mitochondrial damage, which consequently leads to sequential organ failure.\(^5,6\) The role of ascorbic acid in septic patients is complicated and not well understood, including its oxidation resistance and anti-inflammatory properties, cortisol retention, inhibition of nitric oxide synthase, and upregulation of the production of catecholamines in the brain and adrenal medulla.\(^7\)

In recent years, clinical trials have reported that intravenous vitamin C has shown the potential to reduce organ damage caused by sepsis and improve patient survival rates. Fisher et al.\(^8\)–\(^10\) demonstrated that vitamin C could reduce organ damage and improve the survival rate of mice with sepsis. However, the exact role of ascorbic acid as salvage therapy in septic patients is still unclear. Therefore, we assessed the efficacy of vitamin C on mortality among septic patients.

Materials and methods

The present meta-analysis was performed and reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.

We followed the methods of Jiang et al.\(^11\) The purposes of their study made the structure of the article concise.
Registration and protocol

This meta-analysis was registered on PROSPERO. The registration number is CRD42019130027.

Inclusion criteria:
Patients: Adult critically ill patients with sepsis and septic shock
Intervention: vitamin C (regardless of the dose, duration and initial time)
Comparison: Placebo
Outcomes: 28-day mortality. The secondary outcomes were ICU length of stay, the dose of vasopressors and adverse events.
Studies: Randomized controlled trials

Retrieval strategy: vitamin C, ascorbic acid, ascorbate, antioxidant, critically ill, intensive care, critical care, intensive care unit, sepsis, septic shock, randomized controlled trials (RCTs), clinical trial

Data source and literature search

The PubMed, Embase and Cochrane Library databases were searched from inception to December 31 2019. ClinicalTrials.gov was also searched for ongoing or unpublished studies.

Study selection and data extraction

Two reviewers performed the study selection. First, we excluded duplicates using Endnote software. Then, we excluded irrelevant literature by reading titles and abstracts. Finally, we read the full texts of each relevant article to determine which studies were eligible. The same two reviewers independently extracted the data from each eligible study, including characteristics of patients, interventions, comparisons, endpoints, and other related items that were essential for quality evaluation. Any disagreements were resolved by discussion or consultation with the third reviewer.

Study quality evaluation

The quality of the included literature was evaluated based on the following criteria: sequence generation, allocation concealment, blinding of patients and personnel, blinding of outcome assessors, incomplete outcome data, and selective reporting. Each criterion was classified as low risk, unclear risk, or high risk.

Statistical analysis

All statistical analyses were performed using SPSS 19.0 software (SERIAL NO. 4-2B93D) and RevMan 5.3 (The Nordic Cochrane Centre, The Cochrane Collaboration, Copenhagen, Denmark). The odds ratio (OR) was used to analyse dichotomous data, and the standard mean difference (SMD) was used to analyse
continuous data. The heterogeneity between studies was assessed using the $I^2$ test and the chi-square test. $p < 0.05$ and $I^2 \geq 50\%$ indicated significant heterogeneity, and thus, the random effects model was used. Otherwise, the fixed effects model was used.

**Literature selection process**

A total of 328 studies were retrieved according to the search strategy. There were 178 duplicate studies, 95 reviews, and 46 non-RCTs (Figure 1). Ultimately, nine articles were included (Table 1). All included papers were randomized controlled trials. We retrieved an additional 34 study protocols from ClinicalTrials.gov.

- Meta-analysis procedure:
  - The primary outcome: 28-day mortality
  - The secondary outcomes:
    - The ICU length of stay
    - The dose of vasopressors
  - Adverse events
Publication bias was assessed via funnel plots; a visual inspection of the plots revealed no potential bias (Figure 2).

Results

A total of nine randomized controlled trials (RCTs)\textsuperscript{12–20} were enrolled in this meta-analysis (Figure 1). A total of 584 patients were enrolled (301 in the intervention
group and 283 in the control group). All the patients in the experimental group were given vitamin C, and patients in the control group were given a placebo (e.g. a 5% glucose injection). A funnel plot was used to assess publication bias, and a visual inspection of the plot revealed no potential bias (Figure 2). The meta-analysis showed that there was a statistically significant difference in mortality between the experimental group and the control group (fixed effects OR = 0.60 95% CI [0.42, 0.85], \( p = 0.004 \)) (Figure 3). The ICU length of stay was not significantly different between the experimental group and the control group (SMD = -0.33 95% CI [-0.87, -0.20] \( p = 0.23 \)) (Figure 4). Vitamin C led to a reduction in the dose of vasopressors (SMD = -0.88 95% CI [-1.48, -0.29], \( p = 0.003 \)); (Figure 5). Only Fowler’s research\(^{14}\) reported that no patient in the low- or high-dose ascorbic acid treatment arms of this study suffered any identifiable adverse events. The baseline information about the nine trials is listed in Table 1. All of the trials has different levels of bias (Figure 3).

**Discussion**

There have been many studies on the application of vitamin C in critically ill patients, but our meta-analysis mainly focused on whether using vitamin C to treat patients with sepsis and septic shock could improve mortality and related prognostic indicators. The included studies were all randomized controlled studies with the highest level of evidence. To our knowledge, previous studies have not discussed adverse reactions related to this treatment in detail. In addition, we also included the latest study published by Fowler et al. in 2019. Recent studies\(^{21-24}\) have shown that acute disease, endotoxaemia, and sepsis can lead to rapid vitamin C deficiency, which is characterized by low levels of both serum and intracellular vitamins. Patients with severe sepsis\(^{21,25,26}\) usually have very low or undetectable serum vitamin C levels, resulting in acute scurvy. In recent years, an increasingly focused eye has been on the metabolic recovery of critically ill patients with vitamin supplementation. Marik et al.\(^{26}\) found that “HAT Rx”, that is, the early application of vitamin C, hydrocortisone and thiamine, can effectively prevent the progression of organ dysfunction in septic patients and reduce mortality. Other studies\(^{27}\) have shown that the application of vitamin C could significantly shorten the length of mechanical ventilation as well as the ICU length of stay in critically ill patients. However, the efficacy of using vitamin C as a new salvage therapy in severe patients is unclear. Recently, Carr et al.\(^{28}\) showed that 100% of sepsis patients have low vitamin C levels, 88% have vitamin C deficiency diseases, and 38% have vitamin C deficiency. de Grooth et al.\(^{29}\) confirmed that a low serum vitamin C concentration is associated with the severity of organ failure and mortality and can predict the development of multiorgan failure. However, there have been few studies on whether vitamin C supplementation can reduce mortality in septic patients. In our meta-analysis of nine RCTs, the application of vitamin C improved the mortality of septic patients and reduced the dose of vasopressors.
Figure 3. Results of the meta-analysis on mortality.
### Figure 4.
Results of the meta-analysis on ICU length of stay.

![Figure 4](image)

### Figure 5.
Results of the meta-analysis on the dose of vasopressors.

![Figure 5](image)
However, the ICU day between the experimental group and the control group was not significantly different.

**Limitations**

There were still some limitations in this meta-analysis. First, there were only nine RCTs, and 584 patients were enrolled. Second, the dosage, duration, and interval of vitamin C were different in each group, and the follow-up times of the studies enrolled in our research varied. However, we also note that the total amount of vitamin C used in the included studies was at least 3 g/d, regardless of the duration or dose. We also searched ClinicalTrials.gov, and among those ongoing studies, Donnino et al. is currently conducting an RCT (NCT03389555) on the application of vitamin C among 200 patients sepsis. All of the above limitations may have affected the results of our meta-analysis. To obtain more reliable results, larger samples and more high-quality RCTs are needed to verify these findings. In addition, high-dose vitamin C may result in uric acid salt in acid salt stones, dizziness, syncope, diarrhoea, red skin, and other side effects, such as nausea and vomiting. However, only Fowler’s study\(^{14}\) reported the side effects of using vitamin C. Hence, future studies should examine the potential side effects.

**Conclusion**

This meta-analysis demonstrated that using vitamin C (compared to placebo) to treat patients in septic shock led to a reduction in ICU mortality (OR = 0.60 95% CI [0.42, 0.85], \(p = 0.004\)) and a reduction in the dose of vasopressors (SMD = \(-0.88\) 95% CI \([-1.48, -0.29]\), \(p = 0.003\)). However, the ICU length of stay was not significantly different between the two groups. Therefore, multicentre and high-quality RCTs are needed to further clarify the safety and effectiveness of using vitamin C to treat patients with sepsis and septic shock.

**Declaration of conflicting interests**

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**Trial registration**

This meta-analysis was registered on PROSPERO. The registration number is CRD42019130027.
Supplemental material

Supplemental material for this article is available online.

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