ORIGINAL RESEARCH

Impact of Vitamin C on Inflammatory Response and Myocardial Injury in Sepsis Patients

Na Jiang, MM; Nan Li, MM; Jing Huang, MM; Kejuan Ning, MM; Hui Zhang, MM; Haobing Gou, MM; Ruirui Zhang, MM

ABSTRACT

Background • Amidst the complexities of sepsis-induced inflammatory responses and myocardial injury, this study investigates the therapeutic potential of vitamin C in mitigating sepsis complications. The findings offer crucial insights into the prospective use of vitamin C, shaping future strategies for enhanced patient care.

Objective • To investigate the impact of vitamin C on the inflammatory response and myocardial damage in individuals with sepsis.

Methods • A total of 83 sepsis patients treated in our hospital from January 2021 to January 2023 were randomly divided into a control group (n=41, receiving basic treatment) and a study group (n=42, receiving vitamin C in addition to basic treatment). To evaluate the impact of treatment, we compared organ dysfunction, inflammatory response index, myocardial injury index, and morbidity/mortality rates before and after the intervention in both groups. It allowed for a comprehensive analysis of the treatment's effects on these key parameters.

Results • After therapy, the study group exhibited lower SOFA ratings compared to the control group ($P < .05$). Levels of Hypersensitive C-reactive Protein (hs-CRP), Tumor Necrosis Factor (TNF), High Mobility Group Protein B1 (HMGB1), Creatine Kinase Isoenzyme (CK-MB), Troponin I (cTnI), and B-type brain natriuretic peptide (BNP) were significantly lower in the study group than in the control group after treatment ($P < .05$). The study group also demonstrated a lower morbidity and mortality rate (9.52%) compared to the control group (29.27%) ($P < .05$).

Conclusions • Vitamin C supplementation holds significant therapeutic value, contributing to reduced inflammatory response, myocardial injury, morbidity, and mortality rates in sepsis patients. This intervention enhances clinical efficacy, fostering disease regression. (*Altern Ther Health Med.* 2024;30(10):427-431).

Na Jiang, MM; **Nan Li**, MM; **Jing Huang**, MM; **Kejuan Ning**, MM; **Hui Zhang**, MM; **Haobing Gou**, MM; **Ruirui Zhang**, MM, Department of Critical Care Medicine; No. 521 Hospital of Norinco Group; Xian, Shaanxi; China.

Corresponding author: Ruirui Zhang, MM
E-mail: zhangruirui1020@163.com

INTRODUCTION

Sepsis is a systemic inflammatory response syndrome that results from a dysregulated host response to infection and commonly complicates severe trauma and surgery.[1,2] It is characterized by an excessive release of inflammatory mediators, contributing to clinical morbidity and a mortality rate of up to 17%.[2] Acute renal failure secondary to sepsis manifests in approximately 50% of patients, elevating the overall morbidity and mortality rate to 26% without prompt and effective treatment of sepsis.[3,4] Furthermore, sepsis can lead to septic shock and multiple organ dysfunction syndrome.

The pathophysiology of sepsis is intricate, involving an imbalanced pro/anti-inflammatory response, immunosuppression, oxidative stress, and various other contributing factors.[3] Early sepsis is associated with the substantial generation of oxygen-free radicals, inducing oxidative stress and exacerbating organ damage. Therefore, anti-oxidative radical drugs emerge as a crucial avenue in sepsis treatment.[5]

Vitamin C, a potent antioxidant, effectively inhibits the production of oxygen free radicals, mitigating oxidative stress, reducing tissue damage, and presenting itself as a promising drug for sepsis treatment.[6] While vitamin C is recognized for its antioxidant properties, limited research has explored its potential in sepsis treatment. Concurrently, the inflammatory response forms the primary pathological basis of sepsis.[7]

Myocardial injury, a frequent sepsis complication,[8] directly influences body hemodynamics, impacting prognosis negatively. Therefore, it is crucial to determine the stage of sepsis to enhance treatment efficacy and assess potential regression. It involves comparing levels of inflammatory response and myocardial damage for a comprehensive evaluation.

This study focuses on the role of vitamin C in treating sepsis, specifically addressing inflammatory response and

cardiac injury in a group-controlled format. The aim was to provide a reliable and informative reference for the clinical management of sepsis, contributing to a more trustworthy and instructive clinical framework for dealing with this condition.

MATERIALS AND METHODS

Study Design

We randomized 83 sepsis patients admitted to our hospital from January 2021 to January 2023 into two groups: the control group (n=41) received only basic care, and the study group (n=42) received supplemental vitamin C in addition to basic care. The study received approval from the ethics committee, and each participant provided informed consent.

Inclusion and Exclusion Criteria

Inclusion criteria were as follows: (1) Participants meeting the diagnostic criteria for sepsis;[9] (2) having undergone complete treatment at our facility; and (3) possessing an acute physiological and chronic health status score of II≥12. Exclusion criteria were as follows: (1) Individuals with comorbid cardiac conditions like coronary heart disease; (2) renal dysfunction such as chronic kidney disease; (3) immune system disorders; (4) malignant hematological diseases like leukemia; (5) long-term use of hormones or immunosuppressive drugs; (6) comorbid tumors; (7) those in pregnancy or lactation; and (8) those who have taken vitamin C supplementation within the month preceding the study initiation.

Treatment Protocol: Standard Care

Patients in both groups received standard care: (1) Empirical antibacterial medication: All patients initially received empirical broad-spectrum antibacterial medication. Subsequent treatments were tailored based on microbiological culture results and clinical signs. (2) Vasoactive drug administration: Appropriate vasoactive drugs were administered, with a preference for norepinephrine for patients in septic shock. (3) Mechanical ventilation: A lung-protective ventilation strategy was employed for all patients requiring mechanical ventilation.

(4) Clinical management based on guidelines: Clinical treatment, including pain, agitation, and delirium management, followed the 2013 ICU Guideline-recommended analgesic sedation regimen. (5) Nutritional support: Early enteral nutrition support was provided through continuous nutritional pumping. (6) Deep vein thrombosis prophylaxis: Prophylaxis for deep vein thrombosis was initiated as soon as the patient achieved stability.

Treatment in Study Group. The study group received additional vitamin C on top of basic treatment. Vitamin C Injection (Manufacturer: Shanghai Hyundai Hassan (Shangqiu) Pharmaceutical Co Ltd, Approval No.: Guomao Zizhi H20053054, Specification: 5ml:1g) 3g was dissolved in 250ml of 0.9% sodium chloride solution for intravenous infusion, administered once daily for three days.

Treatment in Control Group. In the control group, a placebo with an equivalent dosage of Vitamin C was incorporated into the basic treatment.

Observation Indicators

SOFA Score for Organ Dysfunction. The SOFA score, encompassing six dimensions (respiratory, circulatory, coagulation, renal, central nervous system, and hepatic system), was employed to assess organ dysfunction before and after treatment. Scores ranging from 0 to 4 were assigned, with higher scores indicating more severe organ dysfunction.

Inflammatory Response Indicators. To assess inflammatory response levels both before and after treatment, blood samples were drawn from elbow veins, centrifuged, and processed to obtain the supernatant. The concentrations of tumor necrosis factor (TNF), high mobility group protein B1 (HMGB1), and hypersensitive C-reactive protein (hs-CRP) were then measured.

Myocardial Injury Indicators (Pre- and Post-Treatment). Elbow venous blood samples were obtained, centrifuged, and processed to extract the supernatant. Troponin I (cTnI) levels were determined using the rate technique, Creatine Kinase Isoenzyme (CK-MB) levels were measured using the immunosuppressive method, and B-type brain natriuretic peptide (BNP) levels were determined using the immunofluorescence method.

Morbidity and Mortality. Morbidity and mortality rates for both groups were recorded, and the corresponding rates were calculated.

Statistical Analysis

Statistical evaluation of the data findings was conducted using SPSS 23.0 software (IBM, Armonk, NY, USA). The *t* test was employed for comparing measurement data between groups, while the paired *t* test was utilized for assessing measurement data before and after therapy. Group comparisons were made using the chi-square test (χ^2) for count statistics, expressed as rates. The threshold for statistical significance was set at $P < .05$.

RESULTS

Demographic Analysis

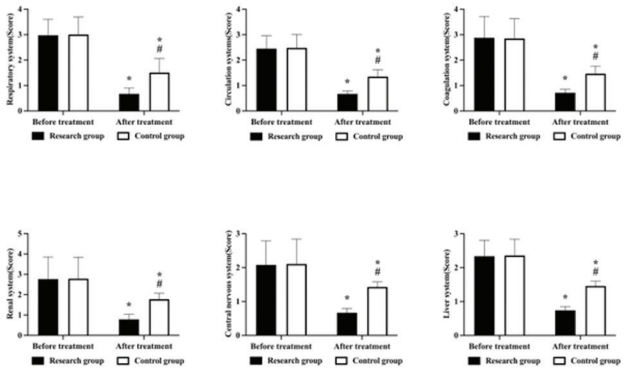
When analyzing clinical data, both age and gender were taken into careful consideration for a comprehensive comparison between the two groups. The outcomes revealed no statistically significant differences between these demographic factors ($P > .05$); refer to Table 1.

Table 1. Comparison of Clinical Information of The Two Groups

Group	n	Age (year)	M/F
Research Group	42	53.25±13.21	22/20
Control Group	41	53.28±13.18	22/19
χ^2 or t	-	0.010	0.014
P value	-	.992	.907

Note: Clinical information comparison between the research and control groups, including sample size (n), mean age with standard deviation ($\bar{x} \pm s$), and gender distribution (M/F ratio). The statistical tests conducted include a chi-square test (χ^2) or *t* test (*t*) as appropriate, with corresponding *P* values.

Figure 1. Changes in the Degree of Organ Dysfunction Before and After Treatment. (A) Changes in the Respiratory System. (B) Changes in the Circulatory System. (C) Changes in the Coagulation System. (D) Changes in the Renal System. (E) Changes in the Central Nervous System. (F) Changes in the Hepatic System.



Note: Subfigure A represents the changes in different organ systems (respiratory, circulatory, coagulation, renal, central nervous, and hepatic) before and after treatment. The symbol "#" denotes statistical significance ($P < .05$) compared with the same group before treatment, while "*" indicates statistical significance ($P < .05$) compared with the control group.

Comparison of Organ Dysfunction Severity

After treatment, both groups exhibited a reduction in SOFA scores. Notably, the research group displayed significantly lower SOFA scores compared to the control group ($P < .05$), see Figure 1A–1F. Importantly, there was no statistically significant variation in all SOFA scores between the two groups before treatment ($P > .05$).

Comparison of Inflammatory Response Indicators

Prior to treatment, no significant differences were observed in hs-CRP, TNF-α, or HMGB1 levels between the two groups ($P > .05$). Post-treatment, both groups demonstrated a reduction in inflammatory response indices, with levels of hs-CRP, TNF-α, and HMGB1 in the study group being notably lower than those in the control group ($P < .05$), see Figure 2A–2C.

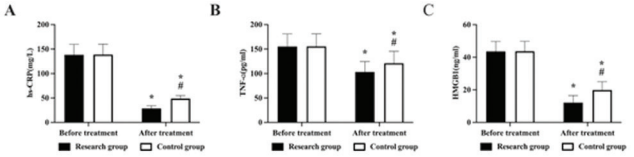
Comparison of Myocardial Injury Indicators

After treatment, both groups exhibited a reduction in levels of myocardial injury indicators. Notably, the research group displayed significantly lower levels of CK-MB, cTnI, and BNP compared to the control group ($P < .05$), see Figure 3A–3C. Importantly, there was no significant variation in the levels of CK-MB, cTnI, and BNP between the two groups before treatment ($P > .05$).

Morbidity and Mortality Rates

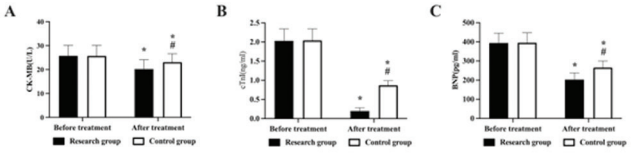
The study group exhibited lower morbidity and mortality rates compared to the control group ($\chi^2 = 5.198$, $P < .05$). Among the 42 patients in the study group, four succumbed to the disease, resulting in a mortality rate of 9.52%. In contrast, the control group, comprising 41 patients, experienced a higher mortality rate, with twelve patients (29.27%) passing away due to the disease, refer to Table 2.

Figure 2. Changes in Inflammatory Response Indicators Before and After Treatment. (A) Changes in hs-CRP (B) Changes in TNF-α (C) Changes in HMGB1.



Note: The figure depicts alterations in inflammatory response indicators before and after treatment, focusing on high-sensitivity C-reactive protein (hs-CRP), tumor necrosis factor-alpha (TNF-α), and high mobility group protein B1 (HMGB1).

Figure 3. Changes in Myocardial Injury Indicators Before and After Treatment. (A) Changes in CK-MB (Creatine Kinase Isoenzyme) (B) Changes in cTnI (Supernatant Troponin I) (C) Changes in BNP (B-type Brain Natriuretic Peptide).



Note: The figure illustrates variations in myocardial injury indicators before and after treatment, focusing on creatine kinase isoenzyme (CK-MB), supernatant troponin I (cTnI), and B-type brain natriuretic peptide (BNP).

Table 2. Morbidity and Mortality Rates Comparison

Group	Total (n)	Mortality (n)	Mortality Rate (%)
Study Group	42	4	9.52
Control Group	41	12	29.27

Note: Comparison of morbidity and mortality rates between the study group and the control group. Mortality rates are presented as the number of deaths (n) and the corresponding percentage (%). Statistical significance was observed with $\chi^2 = 5.198$, $P < .05$.

DISCUSSION

Sepsis has become a global health challenge in the 21st century, characterized by its complex pathogenesis, diverse population impact, and elevated acute mortality rate.[10] The rising prevalence of sepsis is attributed to factors such as accelerated global aging, and prolonged hospital stays for critically ill patients, advancements in medical care, and the widespread use of antibiotics, contributing, in part, to heightened bacterial resistance.[11]

Due to global advancements in diagnostic techniques and organ support therapy, sepsis mortality rates have gradually decreased to approximately 40%. However, the death rate in septic shock remains alarmingly high, reaching up to 60%.[10-12] This higher rate emphasizes the critical nature of the current state of sepsis treatment.[12] Over the past four decades, more than 100 clinical trials have been conducted in pursuit of novel medications and therapies for severe sepsis and septic shock, yet only a few have proven successful. There

is an urgent need for new, effective, safe, and cost-effective treatment options for sepsis.

Vitamin C, an indispensable water-soluble vitamin, presents a multitude of benefits encompassing antioxidant, anti-inflammatory, immunomodulatory, hemodynamic improvement, and protection of endothelial barrier function. Extensively utilized in clinical settings, vitamin C demonstrates considerable potential in addressing a range of health issues. Borran et al.[13] reported its efficacy in clearing creatinine accumulation and improving renal function. In the realm of sepsis, Carr et al.[14] discovered that all patients in septic shock exhibited reduced vitamin C levels, with a staggering 88% experiencing vitamin C levels below 23 μmol/L, indicating deficiency, and 38% suffering from severe vitamin C deficiency (levels below 11 μmol/L).

Marik et al.[15] suggested that vitamin C levels in sepsis decrease due to reduced intake, absorption, and increased metabolism. Supplementation with exogenous vitamin C proves beneficial in reducing the mortality risk associated with sepsis. Individuals with markedly low vitamin C levels often manifest multiple organ failures, suggesting the potential efficacy of using vitamin C in the treatment of sepsis.

Our study revealed that post-treatment, three inflammatory response markers, including hs-CRP, TNF-α, and HMGB1 levels, were lower in the study group compared to the control group. This finding demonstrates the potential of vitamin C to mitigate the severity of the inflammatory response in sepsis. The primary pathological cause of sepsis is an inflammatory response. When the regulation of pro-inflammatory factors is imbalanced in patients after the onset of the illness, a cytokine storm results, altering the permeability of vascular endothelial cells and causing coagulation dysfunction, heightened hemodynamic instability, and an increased risk of mortality.[16,17]

The early identification and prompt intervention of the inflammatory response are crucial priorities in halting the progression of sepsis. Excessive activation of nuclear factor-κB (NF-κB) is closely linked to cytokine storm production in the initial stages of sepsis. Vitamin C exhibits notable anti-inflammatory effects, capable of inhibiting NF-κB activation by preventing TNF-α-induced inhibitory κ-B kinase phosphorylation through p38 mitogen-activated protein kinase induction.[18] Furthermore, vitamin C demonstrates inhibitory effects on late pro-inflammatory cytokines HMGB1 and hs-CRP. Thus, incorporating vitamin C into the sepsis therapy regimen may contribute to mitigating the inflammatory response.

Our study explored the influence of vitamin C on cardiac damage indicators in sepsis patients. The results underscored the pivotal role of vitamin C in reducing myocardial injury in sepsis. Post-therapy, levels of all three myocardial injury indicators, including CK-MB, cTnI, and BNP were lower in the study group compared to the control group. The primary mechanism triggering myocardial injury in sepsis is the generation of substantial amounts of oxygen-free radicals.

Oxygen free radicals have the potential to assault cell and subcellular organelle membranes, initiating lipid peroxidation, disrupting the structure of these membranes, fostering apoptosis, and exacerbating myocardial injury.[19,20] Vitamin C, a potent antioxidant, has demonstrated its capability to neutralize 100% of oxygen radicals in the blood when administered in sufficient quantities, thereby reducing oxidative stress.[21]

Notably, higher oxidative stress responses are associated with lower plasma levels of vitamin C. Consequently, vitamin C supplementation can swiftly elevate plasma concentrations, compensating for the depletion during oxidative stress and thereby diminishing the likelihood of organ damage. The efficacy of Vitamin C in treating sepsis, evident in its ability to reduce myocardial damage and inflammatory response, is underscored by the study's outcomes.

The study also highlighted vitamin C's role in reducing organ dysfunction, as evidenced by lower SOFA scores in the study group. Importantly, the study group exhibited lower morbidity and mortality rates, emphasizing the potential clinical benefit of incorporating vitamin C into sepsis treatment protocols. These findings collectively suggest that vitamin C holds promise as adjunctive therapy in the comprehensive management of sepsis, offering a multifaceted approach to addressing inflammatory response, myocardial injury, and overall organ dysfunction.

Study Limitations

Several limitations need to be acknowledged in this study. The small number of cases may increase the susceptibility to chance effects and limit the generalizability of the findings. Additionally, the optimal dosage of vitamin C for treating sepsis was not explicitly investigated, leaving a gap in understanding the dose-response relationship. Future research should prioritize expanding the sample size to enhance statistical robustness and facilitate a more comprehensive analysis. Moreover, investigating the optimal dosage of vitamin C in the treatment of sepsis will be crucial for providing a more nuanced and practical reference for therapeutic interventions in septic patients.

CONCLUSION

In conclusion, the incorporation of vitamin C into the basic treatment approach proves to be a pivotal strategy in the comprehensive management of sepsis. This study's findings underscore the multifaceted benefits of vitamin C supplementation, revealing its role in reducing the inflammatory response, mitigating myocardial injury, and significantly reducing both morbidity and mortality rates. The observed improvement in clinical efficacy and promotion of disease regression further emphasizes the substantial clinical application value of vitamin C in the context of sepsis treatment. These outcomes collectively advocate for the integration of vitamin C as an adjunctive therapeutic measure, offering a promising avenue to enhance the overall outcomes and prognosis for patients struggling with the complexities of sepsis.

CONFLICTS OF INTEREST
The authors report no conflict of interest.

FUNDING
None.

AVAILABILITY OF DATA AND MATERIALS
The data that support the findings of this study are available from the corresponding author upon reasonable request.

AUTHOR CONTRIBUTIONS
Na Jiang, MM, and Nan Li, MM, have equal contributions to this work.

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