Original Communication

The Protective Effect of Vitamin C Targeting Oxidative Stress on Renal Function in Patients with Septic Acute Kidney Injury: A Prospective, Randomized Controlled, Pilot Study

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Abstract

Objective: To explore whether vitamin C supplementation in sepsis patients can reduce the occurrence of acute kidney injury. **Methods**: A prospective, randomized and controlled pilot trial was conducted. All individuals participating in the study received comprehensive initial treatment for sepsis. This involved monitoring lactate levels, ensuring appropriate fluid resuscitation, administering empiric broad-spectrum antibiotics, and using vasoactive medications, with a preference for norepinephrine. If the norepinephrine dosage exceeded 20 µg/min, vasopressin was introduced at a rate of 0.03 U/min to sustain a mean arterial pressure of at least 65 mmHg. The experimental group was given vitamin C (1.5 g every 6 h by intravenous infusion) for 3 consecutive days, while the control group was given placebo. **Results**: A total of 40 patients with sepsis were included in the study following application of the inclusion and exclusion criteria. Patients were randomized into control (n = 20) and experimental (n = 20) groups. No significant differences in baseline characteristics were found between the two groups (all $p > 0.05$). Among the 40 sepsis patients, 5 (25%) in the experimental group and 14 (70%) in the control group developed acute kidney injury, all of whom required support with continuous renal replacement therapy (RRT). The main site of infection was pulmonary, accounting for 70% of cases in the experimental group and 75% in the control group. The most common pathogenic bacteria were gram-negative bacilli (26/40, 65%). The experimental group had a significantly shorter length of stay in intensive care unit (ICU) compared to the control group (11.8 ± 2.7 days vs. 13.9 ± 2.1 days, $p = 0.008$), less frequent use of vasoactive drugs (35% vs. 75%, $p = 0.011$), and less frequent need for RRT within 72 h of admission (25% vs. 70%, $p = 0.004$). However, the mortality rate in ICU was not significantly different (10% vs. 15%, $p = 0.633$). **Conclusion**: The use of vitamin C in patients with sepsis is associated with a reduced incidence of acute kidney injury, although a larger sample size is required to confirm this finding. **Clinical Trial Registration**: This trial was registered at Chinese Clinical Trial Registry (ChiCTR2400093794, https://www.chictr.org.cn/hvshowproject.html?id=265499&v=1.0)

Keywords: sepsis; oxidative stress; acute kidney injury

1. Background

Sepsis is the leading cause of acute kidney injury (AKI), contributing almost half the cases of renal insufficiency in intensive care units [1]. The development of AKI during episodes of sepsis is a significant and independent prognostic indicator of extended hospital stays and in-hospital mortality [2]. Moreover, epidemiological data increasingly suggests that individuals who survive mild or brief episodes of AKI face an increased risk of subsequently developing chronic kidney disease (CKD) and end-stage renal disease [3]. The essential treatment for sepsis currently includes antibiotics, fluid resuscitation, and vasopressor support. Renal replacement therapy (RRT) is advised for patients experiencing severe septic AKI [4]. Nevertheless, these interventions are primarily palliative and aimed at sustaining life with the goal of kidney recovery. Consequently, a deeper understanding of the pathophysiological mechanisms underlying septic AKI is crucial for the development of effective, mechanism-based therapeutic strategies.

Ascorbic acid, commonly known as vitamin C, is a water-soluble vitamin integral to various bodily functions. This antioxidant acts as an electron donor to effectively neutralize free radicals. By inhibiting the NADPH oxidase (NOX) pathway, vitamin C limits the formation of new free radicals, which also increases the activity of other antioxidants [5]. The antioxidant properties of vitamin C can lead to decreased endothelial permeability, thereby improving the function of both microvascular and macrovascular systems, and diminishing cell apoptosis in pathological states [6,7]. Vitamin C also plays a crucial role in the synthesis of endogenous vasopressin, and can influence the responsiveness of patients to this hormone. Consequently, we designed a prospective, randomized and controlled pilot study to investigate whether the administration of vitamin C to patients experiencing sepsis can reduce the incidence of AKI.

Under sepsis conditions, the body's intake and absorption are known to decrease, while metabolism increases, resulting in a lower level of plasma vitamin C [8]. In about 90% of sepsis patients, the plasma vitamin C level is less than 23 µmol/L. Severe vitamin C deficiency can lead to multiple organ dysfunction, while exogenous supplementation of vitamin C is effective at reducing the mortality rate. A randomized controlled trial reported that giving high-dose vitamin C to patients with sepsis can reduce oxidative damage to endothelial cells and other cell types, thereby improving tissue perfusion and oxygenation and reducing subsequent organ dysfunction [9]. Vitamin C is widely used in clinical practice and can protect cell components from reactive oxygen and free radical-mediated oxidative stress responses, while also participating in collagen secretion and the biosynthesis of dopamine and other molecules.

The impact of vitamin C on clinical outcomes in critically ill patients remains controversial, and research findings are inconclusive. A retrospective observational cohort study [10] evaluated the effects of vitamin C treatment on AKI and mortality in patients with sepsis. The electronic medical records of 1390 patients from a single institute were analyzed, with the data revealing that vitamin C treatment was associated with an increased risk of AKI (OR = 2.07, 95% CI [1.46–2.93]) and in-hospital mortality (OR = 1.67, 95% CI [1.003–2.78]) after adjusting for demographic and clinical covariates. When stratifying for intensive care unit (ICU) patients, vitamin C treatment remained a significant risk factor for AKI (OR = 1.61, 95% CI [1.09–2.39]) and did not protect against mortality (OR = 0.79, 95% CI [0.48–1.31]) [11]. Given these reported associations with AKI and mortality, the continued use of high-dose vitamin C in sepsis patients requires further evaluation.

2. Materials and Methods

2.1 Materials

Clinically relevant data including age, sex, SOFA score, APACHE II score, infection site, type of bacterial infection, comorbidities, and vasoactive drug use were collected in tabular form from patients with sepsis and septic shock who were admitted to our hospital between December 2024 and February 2025.

Trial design and sample size calculation: This was a prospective, randomized, and controlled pilot trial. The study was approved by the Ethics Committee of the Second Hospital of Lanzhou University (approval number 2024A-1348). It was registered with the China Clinical Trial Center (registration number ChiCTR2400093794). A priori power analysis was performed by an independent statistician to determine the required sample size. Large effect size was calculated by PASS software Version: 25.0.3 NCSS LLC (Kaysville, UT, USA) and the power for the primary endpoint (incidence of AKI) was calculated based on a two-sided t-test with a significance level of 5%. The power with regard to the co-primary dichotomous endpoints (proportion of subjects with 5% incidence of AKI) was calculated based on a two-sided chi-square test. With a sample size of 40, the study was estimated to have 80% statistical power at the $\alpha = 0.05$ level. Informed consent was signed by the patient or a family member in all 40 cases included in the study. If the patient was unable to complete the signature due to the use of sedative drugs, coma, etc., his or her immediate family members were consulted to provide informed consent.

Inclusion Criteria: the patient met the Sepsis 3.0 diagnostic criteria. Exclusion Criteria: age <18 years, pregnant, had prior renal injury before sepsis diagnosis, or had G6PD. The definition of sepsis-associated AKI was an AKI that occurred within 7 days of sepsis diagnosis.

2.2 Methods

Patients admitted to hospital from December 2024 to February 2025 for sepsis were prospectively enrolled in the study. They were randomly divided into experimental and control groups according to a computer-generated random sequence list that was subsequently placed in a sealed envelope. All study personnel were blind to treatment allocation, and had no influence on whether the participant received vitamin C or placebo. The blank preparation was consistent with the test drug in terms of appearance, shape, odor, and specifications. All patients included in the study received a combination basic treatment for sepsis that included measurement of lactate levels, adequate fluid resuscitation, empiric broad-spectrum antibiotics, and vasoactive drugs. Norepinephrine was used as the preferred vasoactive drug, but when the dosage exceeded 20 µg/min, vasopressin (0.03 U/min) was added to maintain the mean arterial pressure above 65 mmHg. In addition, the experimental group was given vitamin C (1.5 g every 6 h by intravenous infusion) for 3 consecutive days, while the control group was given placebo. The vitamin C infusion mixture was 5 mL:1 g (Shanghai Modern Hasen [Shangqiu] Pharmaceutical Co., Ltd, Shanghai, China. Batch number: National Drug Approval No. H20053054).

Definitions: The diagnostic criteria for AKI were as specified in the KDIGO guidelines [12]. The Sepsis 3.0 guidelines [13] were used to define sepsis.

Primary outcome: The occurrence of AKI, as defined by simultaneous presence of the sepsis consensus criteria (Sepsis 3.0 recommended definition) and the AKI criteria (KDIGO criteria), within 7 days after the diagnosis of sepsis.

Secondary outcomes: Length of stay in ICU, need for vasoactive drug support, number of RRTs required within 72 h of admission, ICU mortality rate, and the levels of IL-6 and Neutrophil Gelatinase-associated Lipocalin (NGAL) as determined by the ELISA detection method.
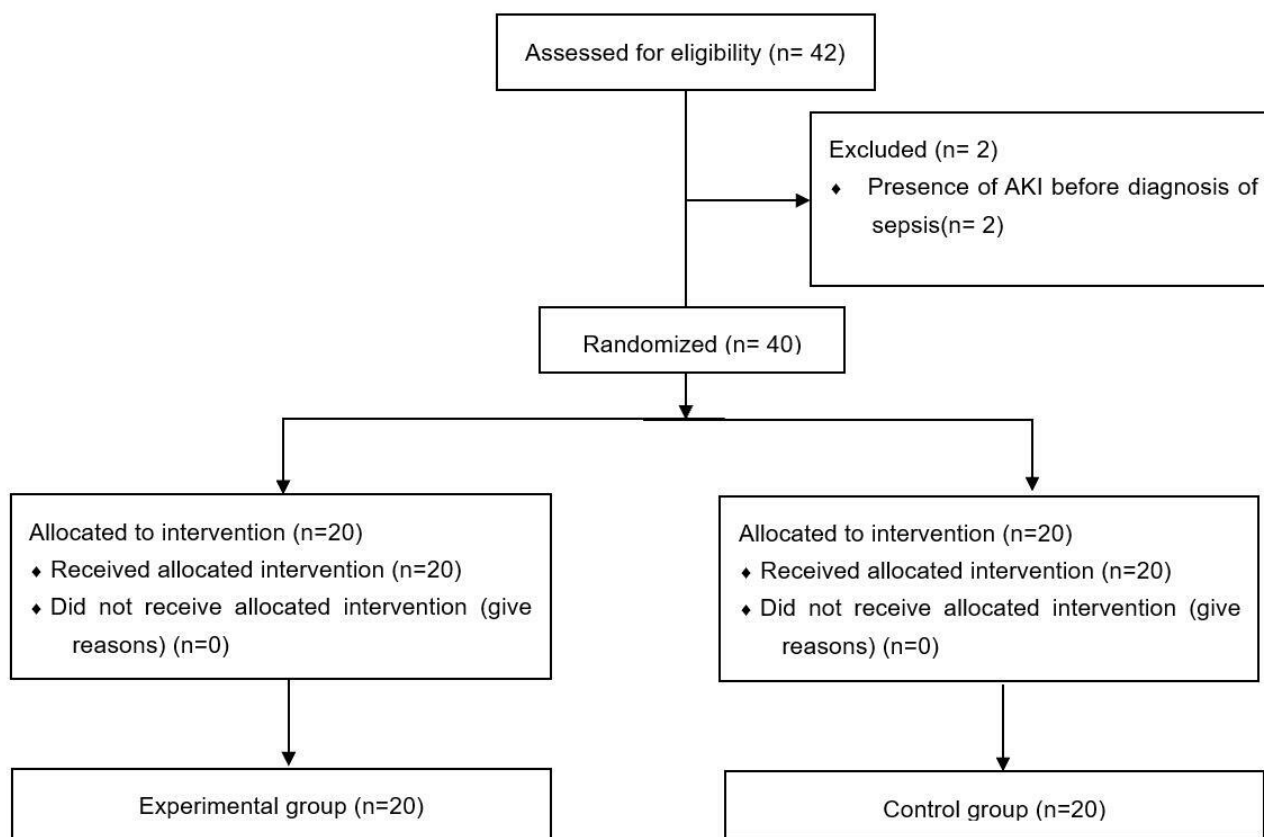
Fig. 1. Flow diagram.

3. Statistical Analysis

Statistical analysis of the data was conducted using SPSS 21.0 software (SPSS Inc., Chicago, IL, USA). The Shapiro-Wilk test and Levene's test were used to assess the normality of data distribution and the equality of variance. For datasets exhibiting a normal distribution, results were expressed as the mean $\pm$ standard deviation ($\bar{x} \pm$ sd). The t test was applied for comparisons between the two groups, while the q-q normal probability plot was employed to assess normality. When the measured data did not follow a normal distribution, the median (M) and interquartile range (QL, QU) was utilized to present the findings. Categorical data were summarized as n (%). Pearson's test was applied for comparison of dichotomous variables between groups, and the Mann-Whitney U test for ordered classifications across multiple groups. All statistical tests were two-sided, with a significance threshold set at $p < 0.05$.

4. Results

Following application of the inclusion and exclusion criteria, a total of 40 patients with sepsis and septic shock were included in the trial, with 20 each in the experimental and control groups (Fig. 1). Table 1 presents the general characteristics for the two groups. Among the 40 sepsis patients included in the study, 5 (25%) in the experimental group and 14 (70%) in the control group devel-

oped AKI, with all requiring continuous RRT support. The main infection site in both groups was pulmonary (70% in the experimental group and 75% in the control group). The main pathogenic bacteria were gram-negative bacilli (26/40, 65%). The average length of stay in the ICU was 11.8 $\pm$ 2.7 days in the experimental group and 13.9 $\pm$ 2.1 days in the control group ($p = 0.008$), the frequency of vasoactive drug use was 35% and 75%, respectively (7 vs. 15, $p = 0.011$), the proportion of RRTs required within 72 h of admission was 25% and 70%, respectively (5 vs. 14, $p = 0.004$), the ICU mortality rate was 10% and 15%, respectively (2 vs. 3, $p = 0.633$), and the IL-6 level was 16.41 $\pm$ 1.93 pg/mL in the experimental group and 39.82 $\pm$ 4.61 pg/mL in the control group ($p = 0.003$). These results are shown in Table 2.

5. Discussion

Vitamin C is an essential cyclic antioxidant that plays a vital role in directly neutralizing reactive oxygen species (ROS) and boosting the levels of endogenous glutathione, thereby helping to regenerate the host's antioxidant defense system. It also acts as an immune enhancer to stimulate macrophage activity [14], while having the capacity to directly inhibit bacterial cations [15,16]. Additionally, vitamin C can reduce the expression of adhesion molecule 1 in human endothelial cells in a dose-dependent manner fol-

Table 1. Baseline Characteristics.

	Experimental group (n = 20)	Control group (n = 20)	*p*-value
Age (years)	55.6 ± 18.5	52.6 ± 18.0	0.607
Sex (male)	12 (60%)	11 (55%)	0.749
Source of Infection			0.881
Pneumonia	14 (70%)	13 (65%)	
BSI	3 (15%)	2 (10%)	
Urosepsis	2 (10%)	2 (10%)	
Other	1 (5%)	3 (15%)	
Comorbidities			
Diabetes	12 (60%)	14 (70%)	0.797
Hypertension	10 (50%)	12 (60%)	0.444
Mechanical ventilation	9 (45%)	8 (40%)	0.756
Arterial lactate level (mmol/L)	2.9 ± 0.5	3.5 ± 0.6	0.001
Procalcitonin level (ng/mL)	35 (28–100)	31 (19–47)	0.069
SOFA score	9.7 ± 2.7	10.7 ± 1.9	0.356
Change in SOFA score at 72 h	–4 (–6 to –1)	–2 (–3 to 0)	0.043
APACHE II score	10.4 ± 1.8	9.8 ± 1.3	0.236
sCr initial (µmol/L)	81.1 ± 13.8	87.5 ± 17.1	0.199
IL-6 (pg/mL)	79.35 ± 6.47	76.44 ± 8.59	0.334
NGAL (ng/mL)	4.9 ± 1.1	5.1 ± 0.9	0.238
Pathogenic bacteria			
Gram-negative bacilli	11	15	0.312
Negative cultures	9	5	0.291

BSI, blood stream infection; sCr, serum creatinine; SOFA, sepsis-related organ failure assessment; APACHE, Acute Physiology and Chronic Health Evaluation; NGAL, Neutrophil Gelatinase-associated Lipocalin.

Table 2. Outcomes.

	Experimental group (n = 20)	Control group (n = 20)	*p*-value
Use of vasoactive drugs	7 (35%)	15 (75%)	0.011
ICU stay (days)	11.8 ± 2.7	13.9 ± 2.1	0.008
Need CRRT at 72 h	5 (25%)	14 (70%)	0.004
ICU Mortality	2 (10%)	3 (15%)	0.633
IL-6 (pg/mL)	16.41 ± 1.93	39.82 ± 4.61	0.003

ICU, intensive care unit; CRRT, continuous renal replacement therapy.

lowing stimulation by TNF. This suggests a potential capacity to mitigate microvascular obstruction by white blood cells and the impairment of microcirculation. Furthermore, vitamin C serves as a crucial auxiliary factor for the synthesis of endogenous vasoconstrictors, such as norepinephrine, and for vessel compression, allowing patients to respond more effectively to vasoactive drug therapies. It is worth noting that critically ill patients often exhibit significantly lower plasma levels of vitamin C [17]. Humans cannot naturally synthesize vitamin C, partially explaining the decrease in vitamin C during sepsis. Because of the presence of saturated intestinal sodium-dependent vitamin C transfer protein (SVCTS), intake through the intestine is insufficient to ensure normal levels of plasma vitamin C, thus requiring intravenous treatment [18].

Monocytes and granulocytes in sepsis patients can be separated by differential sedimentation and centrifuga-tion, and their vitamin C content measured with the dini-trophenylhydrazine method. The concentration of vitamin C in monocytes is 80-fold higher than in plasma, while its concentration in granulocytes is 25-fold higher [19]. Vitamin C is known to play an important role in both monocytes and granulocytes. In clinical trials involving intravenous injection of 1 g of vitamin C in septic shock patients and healthy controls, the vitamin C level decreased more rapidly in the septic shock patients, suggesting higher consumption in these patients and possible accumulation in monocytes and granulocytes [20].

In a randomized double-blind trial in the USA [21], 137 patients with sepsis were randomly divided into treatment and control groups. The treatment group was given vitamin C, hydrocortisone and thiamine, while the control group was given a combination of hydrocortisone and thiamine. The shock reversal time, sequential organ failure

score, procalcitonin clearance rate, and hospitalization time for the two groups were compared to evaluate the therapeutic effect of vitamin C. The SOFA score in the treatment group was significantly lower compared to the control group ($p < 0.01$), while the shock reversal time, PCT-c, and LOS were shorter. Since SOFA and PCT-c are closely related to sepsis-associated organ failure and mortality, these results indicate that supplementation with vitamin C can reduce patient mortality.

While animal studies on early sepsis have shown advantages with vitamin C, its effectiveness in human subjects is still debated. Two small-scale (n = 24 and n = 28), single-center randomized clinical trials demonstrated that intravenous vitamin C doses of between 50 and 200 mg/kg/day led to a reduction in inflammatory biomarkers and SOFA scores [22] and improved patient sensitivity to vasoactive drugs (25 mg/kg every 6 h) [23]. However, in three subsequent multicenter RCTs (VITAMINS [24], ACTS [25] and ATESS [26]), no difference in hospital mortality was observed when vitamin C (6 g/day) was combined with thiamine and corticosteroids, and RRT support was needed at 72 h.

Strengths and Weaknesses

Our study found that patients with sepsis who received venous infusion of 1.5 g of vitamin C for 6 h showed reduced RRT support at 72 h, with only 25% requiring RRT in the experimental group compared to 70% in the control group. Upon admission, NGAL levels were normal in both groups, indicating the absence of any underlying AKI in either group. Since NGAL is an early predictor of AKI, it was not reassessed after treatment. Following the administration of vitamin C, the IL-6 level in the experimental group decreased from 79.35 ± 6.47 to 16.41 ± 1.93 pg/mL, indicating that vitamin C may reduce the incidence of AKI by mitigating the inflammatory response. Vitamin C could also reduce the use of vasoactive drugs in sepsis patients and shorten their length of stay in ICU, although it appears to have no significant effect on the mortality rate. However, a major limitation of our study was the small sample size, and further research is required to validate these results.

6. Conclusion

The administration of vitamin C to patients with sepsis could reduce the occurrence of AKI. However, more studies with a larger sample size are needed to confirm this finding.

Availability of Data and Materials

Data is provided within the manuscript.

Author Contributions

Conducted the study: YC, FF. Collected all data: ML, XES, JQZ. Performed the statistical analysis: YC. All authors have contributed to the editorial changes made to the manuscript. All authors read and approved the final manuscript. All authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

Ethics Approval and Consent to Participate

The study was approved by the Ethics Committee of the Second Hospital of Lanzhou University (approval number 2024A-1348). The study was registered with the China Clinical Trial Center (registration number ChiCTR2400093794). Informed consent was signed by the patient or a family member in all 40 cases included in the study. If the patient was unable to complete the signature due to the use of sedative drugs, coma, etc., his or her immediate family members were consulted to provide informed consent. The study was performed in accordance with the ethical standards as laid down in the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards.

Acknowledgment

Not applicable.

Conflict of Interest

The authors declare no conflict of interest.

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