Original Article

Role of vitamin C in reducing cardiovascular oxidative stress: An in vivo study using sepsis rat models

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Abstract

The aim of this study was to evaluate the effect of vitamin C on reducing cardiovascular oxidative stress in sepsis rat models. An experimental animal study with a post-test control group design was conducted at the Laboratory of Animal Research, Faculty of Veterinary Medicine, Universitas Syiah Kuala, Banda Aceh, Indonesia, from September to December 2023, using 18 male Wistar strain rats (*Rattus norvegicus*). Rats were divided into three groups: control (Group K), lipopolysaccharide 5 mg/kg body weight (BW) (Group L), and lipopolysaccharide 5 mg/kg BW with oral vitamin C (18 mg/day) (Group LC). Rats were euthanized after two weeks with ketamine (15–20 mg/kg intraperitoneally) and cervical dislocation. Blood samples (3 mL) and heart organs were collected. Nitric oxide (NO) levels were measured through enzyme-linked immunosorbent assay (ELISA), and cardiac muscle cells were observed using an Olympus CX21 microscope. The LC group exhibited a significantly lower mean endothelial dysfunction score than the L group ($p<0.001$), although no significant difference in NO levels was observed between L and LC groups ($p=0.262$), indicating that vitamin C did not significantly affect NO levels. This suggests that the improvement in endothelial function observed in the LC group may be mediated through mechanisms other than NO modulation. The MANOVA test revealed that vitamin C administration accounted for 84.8% of changes in endothelial function in the sepsis rat model ($p<0.001$). In conclusion, vitamin C confers a protective effect against severe cardiac and endothelial damage, as evidenced by the amelioration of necrosis, inflammatory cell infiltration, congestion, and vacuolization caused by lipopolysaccharide.

Keywords: Sepsis, oxidative stress, nitric oxide, endothelial dysfunction, vitamin C

Introduction

Sepsis poses substantial morbidity and mortality risks in children with a global prevalence of 8,2% in pediatric intensive care units [1,2]. Sepsis is the leading cause of mortality in developing countries. Studies have been conducted in various hospitals in Indonesia, identifying sepsis-related mortality rates in pediatric patients: 10.7% at Dr. Cipto Mangunkusumo Hospital [3], 66.7% at H. Adam Malik Hospital [4], and 21.8% at Dr. Zainoel Abidin Hospital [5].

Increased oxidative stress is a key factor in cardiovascular disease, with cardiovascular risk factors contributing to endothelial dysfunction [6]. Endothelial dysfunction is prevalent in

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sepsis, highlighting the need for novel therapeutic approaches [7]. Vitamins, crucial micronutrients, play roles in sepsis-related biological pathways and act as antioxidants [8]. During sepsis, plasma vitamin deficiencies are common, and vitamin therapy has shown favorable outcomes in observational and randomized controlled trials in children with sepsis [8]. Vitamin C, a potent antioxidant, also serves as a cofactor in protein and hormone synthesis, energy metabolism, and gene regulation [9].

Previous studies have consistently highlighted the protective effects of vitamin C against cardiovascular complications in various sepsis models, emphasizing its role in reducing oxidative stress and cytokine production [8,10,11]. Shati *et al*. demonstrated that vitamin C administration prevents cardiomyopathy in lipopolysaccharide-induced Sprague Dawley rats by inhibiting cytokine production and oxidative stress [10]. Barabutis *et al*. found that early intravenous vitamin C and thiamine in 47 ICU children significantly prevented progressive organ dysfunction and reduced mortality [11]. Similarly, Wald *et al*. reported that intravenous vitamin C reduced organ dysfunction and endothelial injury in a phase 1 clinical trial [8]. In the previous study, vitamin C improved endothelial dysfunction assessed by arteriolar diameter, anti-inflammatory stoichiometry and several biomarkers as markers of oxidative stress, such as superoxide dismutase (SOD) and malondialdehyde (MDA), while in this study, vitamin C protects lipopolysaccharide-induced cardiac endothelial damage by increasing nitric oxide (NO) levels characterized by reduced cardiac muscle cell necrosis in sepsis model rats. Therefore, vitamin C is one of the therapeutic options for organ dysfunction related to sepsis.

The aim of this study was to evaluate the effect of vitamin C on reducing cardiovascular oxidative stress in sepsis rat models. Vitamin C administration under sepsis can reduce oxidative stress and improve endothelial function. However, to assess its suitability for pediatric use, further research is required through phase II clinical trials involving a small group of pediatric patients with sepsis who will receive vitamin C. This will help evaluate the pharmacological effects observed in phase I trials.

Methods

Study design and animals

This experimental post-test control group study was conducted from September to December 2023 at the Laboratory of Animal Research, Faculty of Veterinary Medicine, Universitas Syiah Kuala, Banda Aceh, Indonesia. Eighteen healthy male Wistar rats (5–10 weeks old; 150–250 g) were randomly assigned into three groups (n=6 per group): control (K), lipopolysaccharide-induced sepsis (L, 5 mg/kg BW), and lipopolysaccharide with oral vitamin C (LC, 18 mg/day). The primary outcomes were serum NO levels and cardiac endothelial histopathology scores.

Animals were housed under standardized environmental conditions (25–27°C; 50–60% humidity; 12:12 light-dark cycle), given *ad libitum* access to food and water, and acclimatized for seven days. The study endpoint was set on day 14 post-treatment. A humane endpoint was predefined and included criteria such as severe weight loss (>20%), persistent lethargy, respiratory distress, unresponsiveness, or inability to eat/drink. Animals reaching these endpoints were euthanized early.

Preliminary study

A preliminary study was conducted to validate the sepsis model. Rats were injected intraperitoneally with 5 mg/kg BW lipopolysaccharide. On day one, they exhibited clinical signs of infection, including tachypnea, tachycardia, piloerection, and elevated body temperature. By day two, bleeding and fluctuating leukocyte counts were observed. Daily clinical evaluations were conducted by a laboratory veterinarian. These findings confirmed that the selected lipopolysaccharide (LPS) dose was effective in inducing sepsis for the main study.

Eligibility and group allocation

Only healthy male rats were included. Exclusion criteria were structural abnormalities, signs of infection, inactivity, or refusal to eat. Group allocation was randomized using Microsoft Excel v2021. No blinding was applied.

Sepsis induction and vitamin C administration

Sepsis was induced via intraperitoneal injection of 5 mg/kg BW LPS. Rats in the LC group received oral vitamin C (18 mg/day) for 14 days. The dosing protocol was based on the validated preliminary study.

Sample collection

At the study endpoint or upon reaching humane endpoints, rats were euthanized using intraperitoneal ketamine (15–20 mg/kg BW), followed by cervical dislocation. Blood (3 mL) was collected from the retro-orbital sinus, centrifuged at 3000 rpm for ten minutes, and serum stored at -20°C. Hearts were excised and fixed in 10% formalin.

Nitric oxide measurement

Serum NO levels were analyzed using a commercial enzyme-linked immunosorbent assay (ELISA) kit (Nitric Oxide Colorimetric Assay Kit, 96T, Singapore), following the manufacturer's protocol. NO levels were interpreted using the control group's mean (100 µmol/L) as the reference.

Histopathological examination

Cardiac tissues were paraffin-embedded, sectioned (5 µm), and stained with hematoxylin and eosin. Histological assessments were performed using an Olympus CX21 microscope to evaluate necrosis, inflammatory infiltration, congestion, and vacuolization. Endothelial injury was scored from 0 (normal) to 3 (severe) based on the percentage of affected myocytes.

Statistical analysis

All data were analyzed using SPSS v25.0 (IBM Corp., Chicago, IL, USA). Normality was tested using the Shapiro-Wilk test. Normally distributed data were analyzed using one-way analysis of variance (ANOVA) with least significant difference (LSD) post hoc testing; otherwise, the Kruskal-Wallis test was used. Wilks' Lambda and Partial Eta Squared were employed to assess multivariate effects and effect sizes. Statistical significance was defined as $p \leq 0.05$.

Results

Preliminary study

Rats administered 5 mg/kg body weight (BW) of lipopolysaccharide intraperitoneally exhibited clinical signs of infection, including tachypnea, tachycardia, piloerection, and elevated body temperature, which is evaluated every day by a veterinarian in the laboratory. On the first day, these signs were observed. By the second day, bleeding and variable leukocyte levels were noted. Based on clinical evaluation, the 5 mg/kg BW lipopolysaccharide injection was effective in inducing sepsis in the rat model.

Characteristic of rats

In both the L and LC groups, which were induced with lipopolysaccharide at 5 mg/kgBW, all 12 rats exhibited piloerection and bleeding, indicating a consistent physiological stress response across the groups. The heart rates varied slightly among the rats, ranging from 500 to 565 beats per minute, with most rats showing rates between 520 and 550 beats per minute. Respiratory rates also showed some variability, generally between 120 and 150 breaths per minute, with the majority of rats having rates of 130 to 150 breaths per minute. Body temperatures ranged from 37.3°C to 39.3°C, with most rats maintaining a temperature around 38.3°C to 39.1°C. A uniform physiological response with slight variations in heart rate, respiratory rate, and body temperature among the rats is presented in **Table 1**.

Table 1. Confirmation of sepsis in groups included with lipopolysaccharide

Rats	Piloerection	Bleeding	Heart rate (beats/minute)	Respiratory rate (breath/minute)	Temperature (°C)
1	+	+	500	126	37.8
2	+	+	550	150	39.1

Rats	Piloerection	Bleeding	Heart rate (beats/minute)	Respiratory rate (breath/minute)	Temperature (°C)
3	+	+	520	130	38.3
4	+	+	520	130	38.7
5	+	+	560	150	39.0
6	+	+	530	140	38.6
7	+	+	530	130	38.6
8	+	+	530	130	38.3
9	+	+	500	120	37.3
10	+	+	565	150	39.3
11	+	+	520	130	38.3
12	+	+	550	150	39.1

Increased oxidative stress was observed in the L group, with five of six rats showing reduced NO levels compared to controls. Conversely, the group had elevated NO levels in four of six rats compared to the lipopolysaccharide group, though two of six rats in the lipopolysaccharide group had lower levels, potentially due to insufficient blood samples. The control group had a mean level of 102.96±13.48 ppb, while the L group showed a reduced mean of 66.88±16.59 ppb. The LC group had a mean level of 75.93±9.19 ppb. The *p*-value of 0.001 indicates a significant difference among the groups, with vitamin C mitigating the reduction of NO caused by lipopolysaccharide (**Figure 1**).

The comparison between Group K and Group L showed a significant mean difference of 36.08 ppb (95% confidence interval (CI): 19.54–52.62; $p<0.001$), indicating a substantial decrease in NO levels due to lipopolysaccharide. The comparison between the K group and the LC group also showed a significant mean difference of 27.03 ppb (95%CI: 10.49–43.57; $p=0.003$), suggesting that vitamin C mitigated the reduction in NO levels caused by lipopolysaccharide. However, the comparison between the L group and the LC group yielded a non-significant mean difference of -9.05 ppb (95%CI: -25.59–7.48; $p=0.262$), indicating no statistically significant effect of vitamin C when compared directly to the lipopolysaccharide group.

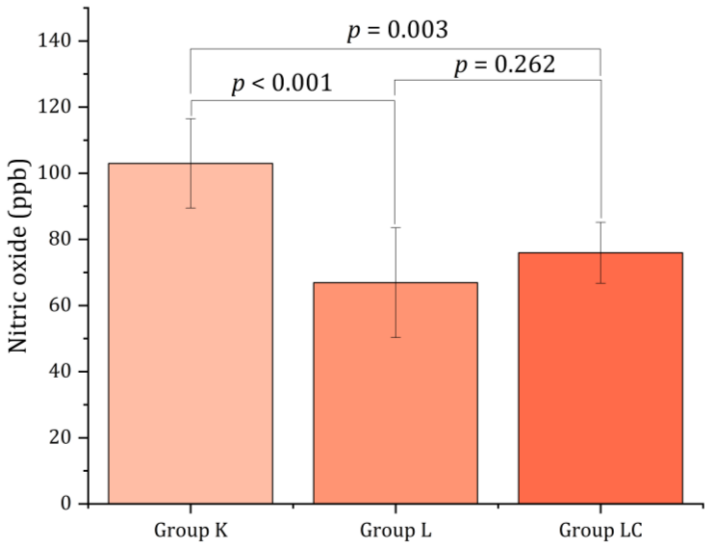

Figure 1. Effect of vitamin C on nitric oxide in LPS-induced septic rats. Group K: control; group L: lipopolysaccharide-induced sepsis; group LC: lipopolysaccharide with oral vitamin C.

Effect of vitamin C on cardiac muscle cell morphology

The K group exhibited normal cardiac muscle morphology with uniformly shaped and sized muscle bundles, well-organized cytoplasm, and non-enlarged nuclei (**Figure 2A**). The L group displayed extensive cardiac muscle damage, including necrosis, inflammatory cell infiltration, congestion, and vacuolization (**Figure 2B**). Conversely, the LC group showed notable improvement in cardiac muscle condition (**Figure 2C**).

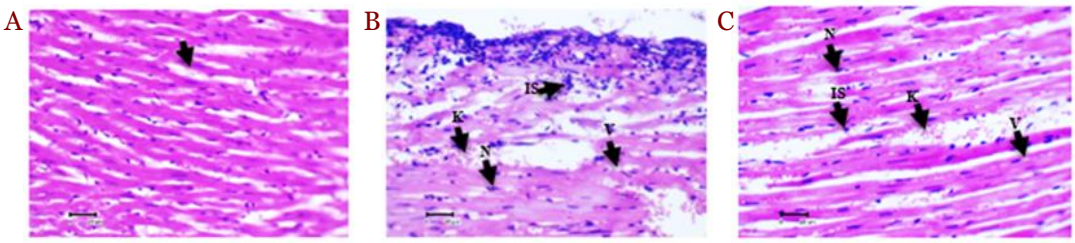

Figure 2. Histopathology of cardiac muscle: (A) Normal cardiac muscle in the control group (K), (B) cardiac muscle in the lipopolysaccharide group (L), and (C) cardiac muscle in the lipopolysaccharide + vitamin C treatment group (LC). N: necrosis; IS: inflammatory cell infiltration; K: congestion; V: vacuolization.

Research shows that the plasma vitamin C concentration in early sepsis is inversely correlated with the degree of multiorgan dysfunction, where high vitamin C concentrations at the onset of sepsis will reduce the risk of multiorgan dysfunction [12]. The effect of vitamin C on endothelial function in LPS-induced septic rats is presented in **Figure 3**, where there is a significant difference between the control group and the L group (p<0.001), and after the administration of vitamin C, there is a significant difference between the L group and the LC group (p<0.001). In this study, the measurement of vitamin C levels was not carried out. Although biochemically, vitamin C functions as an electron donor or reducing agent, forming relatively stable free radicals with a half-life of only a few minutes, a representative diagram of the administration of vitamin C on NO in septic rats shows that vitamin C's effect on NO is limited. This may be caused by inadequate levels of vitamin C.

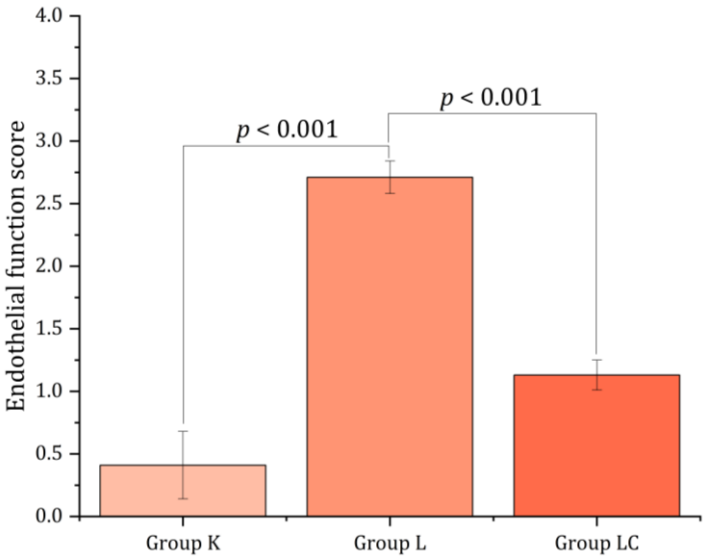

Figure 3. Effect of vitamin C on endothelial function in LPS-induced septic rats. Group K: control; group L: lipopolysaccharide-induced sepsis; group LC: lipopolysaccharide with oral vitamin C.

The control group exhibited a mean endothelial function value of 0.41±0.27. In contrast, the L group showed a significantly higher mean value of 2.71±0.13, indicating impaired endothelial function. The LC group had a mean value of 1.13±0.12, suggesting that vitamin C mitigated the endothelial dysfunction induced by lipopolysaccharide. The comparison between the control and L groups showed a significant mean difference of -2.3 (p<0.001), highlighting the detrimental effect of lipopolysaccharide on endothelial function. Similarly, the comparison between the control and LC groups revealed a significant mean difference of -0.7 (p<0.001), indicating some protective effect of vitamin C. However, despite this protective effect on endothelial function, there was no significant difference in NO levels between the L and LC groups (p=0.262), indicating that vitamin C did not significantly reduce NO levels.

Discussion

Lipopolysaccharide, a key component of Gram-negative bacterial cell walls, was used to induce sepsis in rats [12]. In the present study, rats administered 5 mg/kg BW of lipopolysaccharide intraperitoneally exhibited clinical signs of infection, including tachypnea, tachycardia, piloerection, and elevated body temperature on the first day. By the second day, bleeding and variable leukocyte levels were observed. The 5 mg/kg BW dose was selected based on its significant effect on sepsis. Lipopolysaccharide stimulates inflammatory mediators, which can lead to sepsis and organ damage [16]. Stress factors triggered increased secretion of stress hormones from the adrenal glands, leading to heightened inflammatory biomarkers and clinical symptoms [10]. Under stress, respiratory rate can rise to 150 breaths per minute, heart rate to 550 beats per minute, and rectal temperature may exceed 37.50°C [10].

In the present study, NO levels decreased in rats given lipopolysaccharide, indicating oxidative stress. However, NO levels significantly increased in the group receiving vitamin C compared to the lipopolysaccharide group, emphasizing that vitamin C mitigates the reduction of NO caused by lipopolysaccharides. Sini *et al.* reported that vitamin C administration increased arteriole diameter in sepsis model Wistar rats (p=0.001) [17]. Sepsis alters vasodilatory tone due to changes in NO levels, and vitamin C mitigates this by inhibiting NO synthase and enhancing NO levels. Impaired NO synthesis can lead to vasoconstriction and exacerbate endothelial damage, affecting vital organs such as the heart, kidneys, and brain [18]. Fowler *et al.* reported that vitamin C therapy reduced mortality in sepsis patients from 46.3% to 29.8% (p=0.03) [19]. Shati *et al.* found that high-dose intravenous vitamin C reduced MDA levels, restored SOD activity, and minimized cardiomyocyte damage, suggesting its potential to improve organ dysfunction and reduce inflammation in sepsis [10].

While vitamin C in the present study had a significant impact when compared to the control, its additional protective effect in the presence of lipopolysaccharide was not statistically significant (p=0.05), potentially due to factors such as the route of administration, dose, and duration of therapy (14 days). Low doses of vitamin C may be inadequate to counteract the pathophysiology of sepsis, as they might not provide sufficient antioxidant and anti-inflammatory effects. Optimal dosing should maximize these effects without inducing a prooxidative state [20]. Clinical studies suggest that high-dose intravenous vitamin C, administered every six hours for three days, offers significant benefits in sepsis treatment [20]. This regimen has been associated with improved organ dysfunction and reduced inflammation and vascular injury in patients with sepsis and acute respiratory distress syndrome [20].

The present histopathological findings suggest that vitamin C confers a protective effect against the severe cardiac and endothelial damage caused by lipopolysaccharide, improving both histopathological outcomes and endothelial function. Lipopolysaccharide induces severe pathological changes in cardiac tissue, likely contributing to significant endothelial dysfunction. Vitamin C helps mitigate endothelial dysfunction, possibly by counteracting the inflammatory and oxidative stress mechanisms induced by lipopolysaccharide. Additionally, NO levels and endothelial function were significantly affected by lipopolysaccharide, but vitamin C provided a substantial protective effect, accounting for 84.8% of the variance in changes in these parameters (p<0.001). Aligned with a previous report suggesting that vitamin C enhances endothelial proliferation, cell survival, and vascular integrity [20]. In another previous study, vitamin C was reported to reduce plasma volume loss in sepsis by preventing microvascular permeability [21]. A previous study found that vitamin C improved endothelial function in sepsis rats by reducing nicotinamide adenine dinucleotide phosphate (NADPH) oxidase activity, superoxide production, and increasing endothelial nitric oxide synthase (eNOS) activity and NO formation [22]. A large study consisted of 374,488 patients over ten years demonstrated an inverse relationship between vitamin C intake and coronary heart disease risk [23], and a similar association was observed in Japanese women over a median of 16.5 years [24].

In a meta-analysis of 44 trials with 1,324 participants, vitamin C supplementation (>500 mg/day) was reported to significantly enhance endothelial function [25]. Oxidative stress depletes NO, causing vasoconstriction and impaired oxygen delivery, while vitamin C mitigates these effects by preserving endothelial integrity and reducing reactive oxygen species (ROS)-

induced damage [26]. Shati *et al.* found that vitamin C mitigates endotoxin-induced cardiac injury by repairing heart structures (p=0.005) [10].

This study has several limitations. First, it only examined NO as a marker of oxidative stress, without assessing other biomarkers. Additionally, vitamin C levels were not measured, and direct sampling of endothelial cells posed challenges; therefore, endocardium samples were collected instead.

Conclusion

These findings suggest that sepsis is associated with oxidative stress, as indicated by a decrease in NO levels. Vitamin C mitigated lipopolysaccharide-induced cardiac endothelial damage. However, this effect does not appear to be mediated by restoration of NO levels, as vitamin C did not significantly reduce NO levels. This suggests that the improvement in endothelial function may involve alternative protective mechanisms, such as antioxidant or anti-inflammatory pathways. Vitamin C conferred a protective effect against severe cardiac and endothelial damage, as evidenced by the amelioration of necrosis, inflammatory cell infiltration, congestion, and vacuolization caused by lipopolysaccharide. While NO levels and endothelial function were significantly affected by lipopolysaccharide, vitamin C supplementation provided substantial protection, accounting for 84.8% of the variance in changes to these parameters.

Ethics approval

Ethical clearance approval for the use of animals was obtained (Certificate of ethics) Ref: 272/KEPH/X/2023.

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Conflict of Interest

The author declares no conflict of interest.

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Underlying data

Derived data supporting the findings of this study are available from the corresponding author on request.

Declaration of artificial intelligence use

We hereby confirm that no artificial intelligence (AI) tools or methodologies were utilized at any stage of this study, including during data collection, analysis, visualization, or manuscript preparation. All work presented in this study was conducted manually by the authors without the assistance of AI-based tools or systems.

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