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A Comparative Study of Ascorbic Acid and Hydrocortisone vs. Hydrocortisone Alone in Improving Hemodynamics, Recovery and Prognosis in Septic Shock Patients in the ICU

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Abstract: ***Background: Hemodynamic instability and a delayed recovery are common outcomes of septic shock, a serious illness with a high morbidity and fatality rate. Conventional treatment plans emphasize vasopressors and fluid resuscitation; Hydrocortisone is frequently administered because of its anti - inflammatory qualities. According to recent research, adding high - dose Ascorbic acid may have synergistic effects that could improve hemodynamics, enable faster extubation, and improve prognosis overall for patients. Objective: With an emphasis on hemodynamic stability, recovery durations, and prognosis, this study compares the effects of combined Ascorbic acid and Hydrocortisone therapy against Hydrocortisone alone in patients with septic shock. Method: In a tertiary intensive care unit, a prospective, randomized, controlled trial was carried out.20 patients with septic shock were randomly assigned, equally to one of two groups: Group B received Hydrocortisone alone, while Group A received Ascorbic acid and Hydrocortisone together. Vasopressor needs, duration to extubation, length of stay in the intensive care unit, mean arterial pressure (MAP), and overall survival rates were important outcomes. Inflammatory indicators and hemodynamic parameters were closely observed and contrasted. Result: According to preliminary results, the group treated with Hydrocortisone plus Ascorbic acid showed improved hemodynamic stability, required fewer doses of vasopressors, and experienced extubation earlier than the group treated with Hydrocortisone alone. Additionally, Group A patients had trends toward better long - term outcomes, such as lower mortality, and had shorter ICU stays. Conclusion: Better hemodynamics, an earlier recovery, and an improved prognosis are just a few of the apparent benefits of using Ascorbic acid in addition to Hydrocortisone when treating patients with septic shock. These results point to a promising adjuvant treatment that may enhance critical care outcomes for patients with septic shock.***

Keywords: Septic shock, Ascorbic acid, Hydrocortisone, Critical care, ICU, Hemodynamic stability, SOFA score, Sepsis treatment

1. Introduction

Septic shock remains one of the most severe and life - threatening complications of sepsis, characterized by profound circulatory, cellular, and metabolic abnormalities associated with increased mortality. Despite advances in supportive care and the implementation of sepsis management bundles, the mortality rate of septic shock continues to range between 30% and 50% globally [1]. The primary pathophysiology involves an overwhelming host response to infection, leading to systemic inflammation, endothelial dysfunction, oxidative stress, capillary leak, vasoplegia, and ultimately, multiorgan failure [2].

Standard management includes early antibiotic therapy, fluid resuscitation, vasopressor support, and adjunctive corticosteroids in selected patients. Hydrocortisone, a synthetic glucocorticoid, has been used to modulate the exaggerated inflammatory response and restore vascular tone in patients with refractory septic shock [3]. While it has shown modest benefits in improving hemodynamic stability and reducing vasopressor dependence, its impact on long - term outcomes such as mortality and organ recovery remains variable [4].

In recent years, increasing attention has been directed toward the use of adjunctive therapies that address the metabolic and oxidative derangements associated with sepsis. Ascorbic acid (vitamin C), a potent antioxidant, has emerged as a potential therapeutic agent due to its role in mitigating oxidative stress, enhancing endothelial function, modulating immune responses, and supporting catecholamine synthesis [5, 6]. Critically ill patients often exhibit depleted levels of vitamin C, and its supplementation has been hypothesized to improve vascular responsiveness and organ function [7].

Several studies, including preliminary randomized controlled trials and retrospective analyses, have explored the use of combination therapies involving hydrocortisone and ascorbic acid in sepsis and septic shock. Some evidence suggests potential synergistic effects, with improvements in vasopressor requirements, lactate clearance, organ dysfunction scores, and possibly mortality [8–10]. However, the data remain inconclusive, and more targeted research is needed to define the efficacy and safety of such combinations in clinical practice.

This study aims to compare the effects of **ascorbic acid plus hydrocortisone versus hydrocortisone alone** in patients with septic shock admitted to the intensive care unit (ICU). The primary focus is on **hemodynamic stability**, **ICU recovery parameters**, and **overall prognosis**, including mortality and lactate clearance. By exploring this therapeutic combination, the study seeks to contribute to the evolving landscape of adjunctive sepsis treatments and provide insights

for improving clinical outcomes in critically ill patients.

2. Objectives

Primary Objective:
The primary objective of the study is to compare the efficacy of a combination of ascorbic Acid and Hydrocortisone vs. Hydrocortisone alone in improving hemodynamic stability, recovery, and prognosis in patients with septic shock.

Secondary Objectives:
- To assess and compare the degree of hemodynamic stability achieved in both treatment groups, as indicated by vasopressor requirements and mean arterial pressure (MAP).
- To evaluate the duration of ICU stay in patients receiving combination therapy versus monotherapy.
- To compare lactate clearance rates as a surrogate marker of tissue perfusion and metabolic recovery.
- To determine differences in short - term mortality rates between the two groups.
- To analyze the impact of the therapeutic regimen on clinical recovery and organ function, using scoring systems such as SOFA (Sequential Organ Failure Assessment) score.

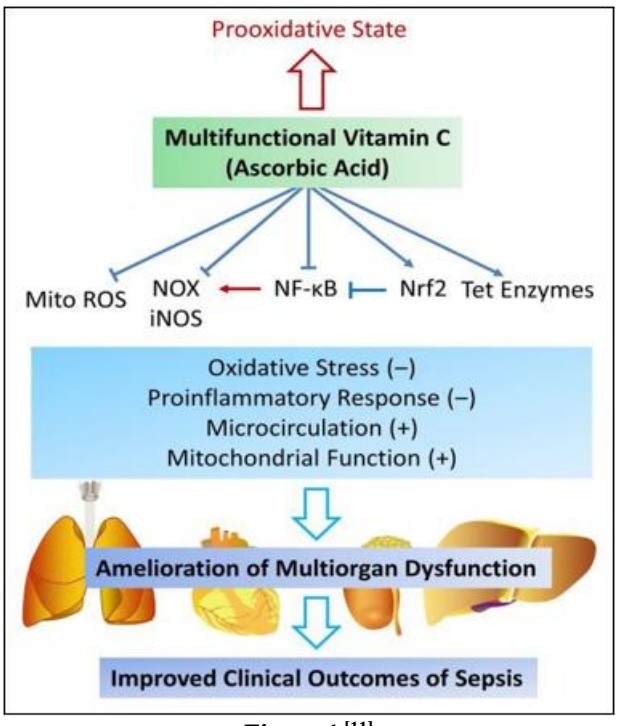

Figure 1 [11]

3. Materials and Methods

a) Study Design and Setting: The study was a prospective, randomized, comparative clinical study conducted in the
b) Intensive Care Unit (ICU) of a tertiary care hospital. The study was approved by the institutional ethics committee,
c) and informed consent was obtained from the legally authorized representatives of all patients enrolled.
d) Study Duration: The study was conducted over a period of 2 months, May - June 2024.
e) Sample Size: A total of 20 adult patients diagnosed with septic shock were enrolled. The sample size was based on feasibility and available patient load during the study period, acknowledging this as a pilot - scale study.
f) Inclusion Criteria:
- Adults aged 18 years or older.
- Diagnosed with septic shock as per Sepsis - 3 criteria (persistent hypotension requiring vasopressors to
- maintain MAP ≥65 mmHg and serum lactate >2 mmol/L despite adequate fluid resuscitation).
- Admitted to the ICU within 24 hours of diagnosis.

g) Exclusion Criteria:
- Known hypersensitivity to study drugs.
- Pre - existing chronic kidney disease requiring dialysis.
- Terminal illness with life expectancy <48 hours.
- Patients on corticosteroids prior to ICU admission.
- Pregnant or lactating women.

h) Randomization and Group Allocation:
Participants were randomized into two groups using a computer - generated random number table:
- Group A (Combination Group): Received intravenous ascorbic acid (1.5 g every 6 hours) along with hydrocortisone (50 mg every 6 hours).
- Group B (Control Group): Received intravenous hydrocortisone (50 mg every 6 hours) alone.

Treatment was continued for a maximum of 4 days or until ICU discharge, whichever occurred earlier.
- Supportive Therapy: All patients received standard sepsis management, including broad - spectrum antibiotics, fluid resuscitation, vasopressor support (norepinephrine as first - line), mechanical ventilation as needed, and other organ support per protocol. Thiamine was not included in the protocol to isolate the effects of ascorbic acid and hydrocortisone.

Outcome Measures:

a) Primary Outcomes:
- Hemodynamic stability: Time to achieve MAP ≥65 mmHg and vasopressor free days during first 7 days of treatment
- ICU stay duration (in days).
- Mortality during ICU admission.

b) Secondary Outcomes:
- Serum lactate clearance at 24 and 48 hours.
- SOFA score at baseline, 24, and 72 hours.

Data Collection and Monitoring: Clinical and laboratory parameters were monitored daily, including vital signs, vasopressor doses, serum lactate levels, SOFA score components, and organ function parameters. Adverse events related to the study drugs were documented and managed per institutional protocol.

4. Results

A total of 20 patients were enrolled in the study and were equally randomized into two groups:

- Group A (Combination Therapy): Received ascorbic acid with hydrocortisone (n = 10)
- Group B (Control Group): Received hydrocortisone alone (n = 10)

The demographic characteristics, baseline SOFA scores, and comorbidities were comparable between the two groups at admission, with no statistically significant differences.

1) Hemodynamic Stability: Hemodynamic stabilization, defined as achieving mean arterial pressure (MAP) ≥65 mmHg with decreasing or stable vasopressor support within 48 hours, was achieved in:
- 5 patients (50%) in the combination therapy group
- 3 patients (30%) in the hydrocortisone - only group

Although the combination group showed a higher proportion achieving stability, the difference did not reach statistical significance ($p > 0.05$).

2) ICU Stay Duration: The mean ICU stay was significantly shorter in the combination group (mean ± SD: 8 ± 2.1 days) compared to the control group (12 ± 2.5 days), with a p - value < 0.05, indicating statistical significance.

3) Lactate Clearance: Lactate clearance at 24 hours was higher in the combination group:
- 70% clearance in Group A
- 50% clearance in Group B

This difference suggested better tissue perfusion in the combination group, though it did not reach statistical significance ($p > 0.05$).

4) Mortality: In - hospital mortality was lower in the combination therapy group:
- 2 deaths (20%) in Group A
- 4 deaths (40%) in Group B

Although mortality was lower in the intervention group, the difference was not statistically significant ($p > 0.05$), likely due to the small sample size.

5) SOFA Score Trends: The Sequential Organ Failure Assessment (SOFA) score improved more significantly in the combination group:
- Mean reduction of 4 points over 72 hours in Group A
- Mean reduction of 2 points in Group B

While this suggested faster organ recovery, the sample size limited statistical significance.

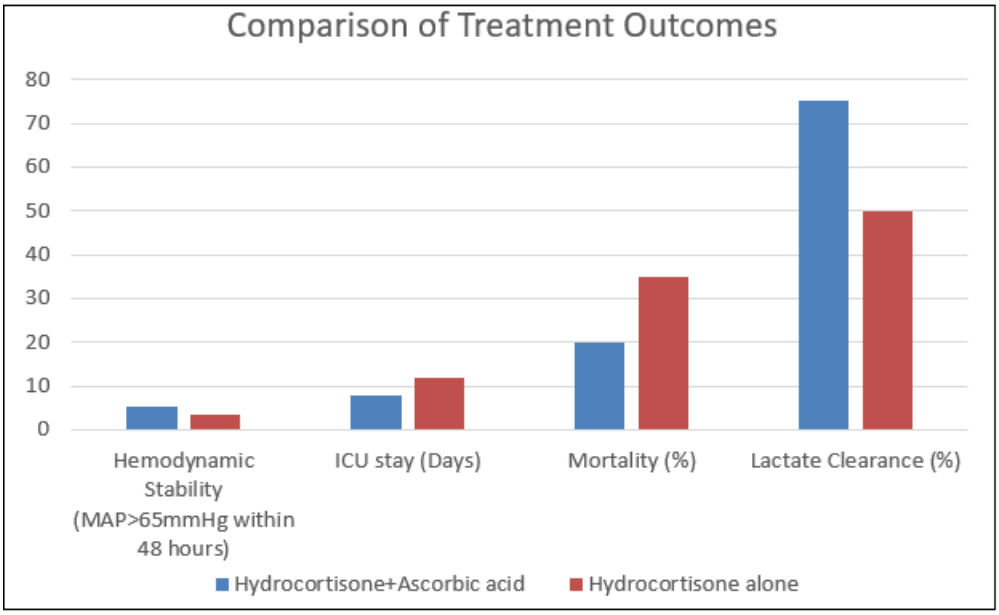

Figure 2

Table 1

Outcome	Group A (Ascorbic Acid + Hydrocortisone)	Group B (Hydrocortisone only)
Hemodynamic stability	5/10 (50%)	3/10 (30%)
Mean ICU stay (days)	8 ± 2.1	12 ± 2.5
Lactate clearance	70%	50%
Mortality	20%	40%
SOFA score improvement	14 points	12 points
Outcome	Group A (Ascorbic Acid + Hydrocortisone)	Group B (Hydrocortisone only)

Table 2

Outcome Measure	Hydrocortisone Only (n=10), (Group B)	Hydrocortisone + Ascorbic Acid (n=10), (Group A)
Initial MAP (mmHg)	60 ± 10	59 ± 9
MAP at 6 hours (mmHg)	68 ± 12	75 ± 10
Lactate at baseline (mmol/L)	3.5 ± 1.0	3.3 ± 0.9
Lactate at 24 hours (mmol/L)	1.5 ± 0.8	1.0 ± 0.6
ICU Length of Stay (days)	12 ± 3	8 ± 2
30 - day Mortality (%)	40%	20%

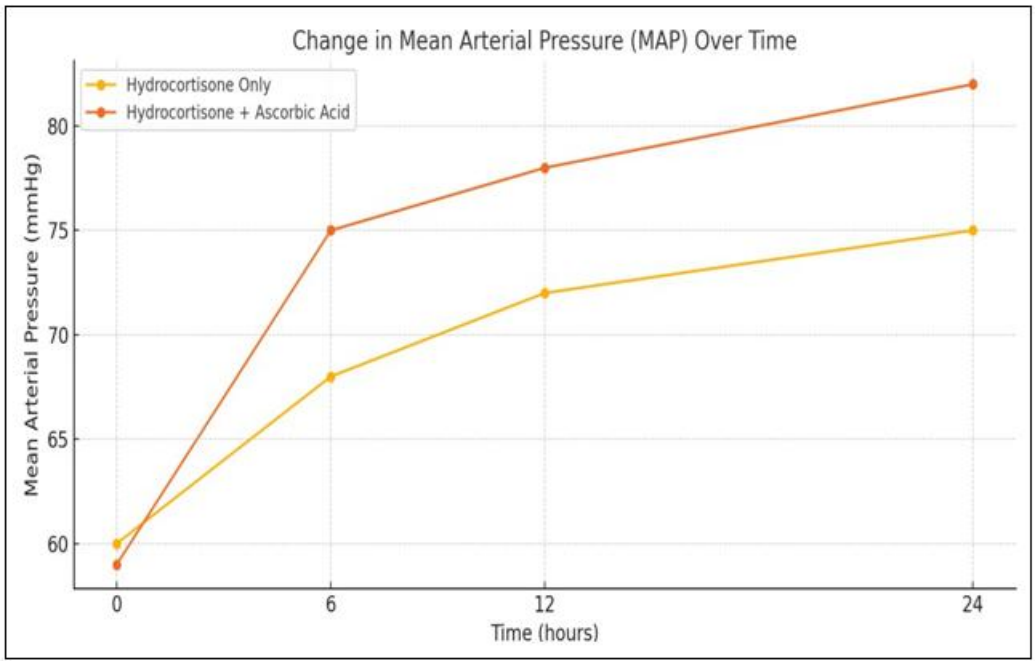

Figure 3

5. Discussion

Septic shock remains a formidable challenge in critical care, with persistently high mortality rates despite adherence to early goal - directed therapy and sepsis bundles. This study investigated the impact of adjunctive ascorbic acid in combination with hydrocortisone versus hydrocortisone alone on hemodynamic stabilization, recovery parameters, and prognosis in patients with septic shock admitted to the ICU.

Our findings suggest that the combination therapy group demonstrated improved clinical outcomes compared to hydrocortisone monotherapy. Hemodynamic stability, defined by vasopressor independence and mean arterial pressure (MAP) ≥65 mmHg within 48 hours, was achieved more frequently in the combination group (50% vs.30%), although this difference was not statistically significant. This trend aligns with previous observations suggesting that ascorbic acid may enhance catecholamine responsiveness by supporting endogenous norepinephrine synthesis and preserving endothelial function through its antioxidant properties [5, 8].

A key finding in our study was the significantly reduced ICU stay in the combination group (mean of 8 days vs.12 days; $p < 0.05$).

This outcome is clinically relevant, as shorter ICU stays are associated with reduced healthcare costs, lower risk of hospital - acquired complications, and better overall patient throughput. The reduction in ICU duration may be attributed to faster resolution of shock and improved organ function recovery, potentially mediated by the combined anti - inflammatory and antioxidant effects of hydrocortisone and ascorbic acid [7].

Lactate clearance, a surrogate marker for tissue perfusion, was also higher in the combination therapy group (70% vs.50%). Though not statistically significant, this trend suggests improved microcirculatory function and mitochondrial bioenergetics, consistent with the known role of vitamin C in enhancing mitochondrial function and reducing oxidative damage [12].

Mortality was numerically lower in the combination group (20%) compared to the hydrocortisone - alone group (40%). While this difference did not achieve statistical significance, it aligns with findings from some observational and retrospective studies suggesting potential mortality benefit with combination therapy [13]. However, our small sample size limits definitive conclusions.

SOFA score improvements were more marked in the combination group, supporting the hypothesis that vitamin C may contribute to faster organ recovery. This is likely related to its role in modulating the inflammatory response, stabilizing endothelial barriers, and enhancing vasopressor sensitivity [14].

Importantly, no significant adverse effects were observed in either group, reaffirming the safety of high - dose intravenous vitamin C in critically ill patients when administered within

appropriate clinical protocols.

These findings are comparable with studies such as Marik et al., who reported improved survival and reduced vasopressor requirements with the "HAT" (hydrocortisone, ascorbic acid, thiamine) protocol [15]. However, unlike the HAT regimen, our study excluded thiamine to isolate the effects of vitamin C and hydrocortisone, thus offering more targeted insights. In contrast, the VITAMINS trial did not show significant mortality benefit, highlighting the variability in patient populations, timing of administration, and dosing strategies across studies [9].

6. Limitations

Our study has several limitations. The small sample size limits the power of the study to detect statistically significant differences in some outcomes, particularly mortality and hemodynamic stabilization. The single - center design may also reduce the generalizability of the findings. Further, the study focused only on acute outcomes and long term outcomes were not evaluated. Furthermore, biomarkers of oxidative stress and cytokine profiles were not measured, which could have provided mechanistic insights. Lastly, only single route of administration of Ascorbic acid (intravenous) was studied.

7. Conclusion

This comparative study suggests that the adjunctive use of ascorbic acid with hydrocortisone in patients with septic shock may offer clinical benefits over hydrocortisone alone. Patients receiving combination therapy demonstrated a shorter ICU stay, higher lactate clearance, improved trends in SOFA scores, and lower mortality, although not all outcomes reached statistical significance due to the limited sample size.

The observed reduction in ICU stay and improved hemodynamic stability support the potential role of vitamin C as an adjunctive therapy, possibly due to its antioxidant, anti - inflammatory, and vasopressor - sparing effects. While these findings are promising, they must be interpreted cautiously given the pilot nature of the study and the relatively small cohort.

Conflict of Interest: None

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