



# The Effect of Hydrocortisone-Ascorbic Acid and Thiamine Therapy on the Outcome of Patients with Sepsis: Prospective Randomized Double-Blinded Controlled Trial

Mostafa Ismail Sharaf <sup>a\*</sup>, Sameh Abd El Khalik Ismaeil <sup>a</sup>,  
Mohamed Mohi El Deen Abo El Yazeed <sup>a</sup>,  
Hala Mohey El-Deen El-Gendy <sup>a</sup>  
and Salah Eldeen Ibrahim Alsherif <sup>a</sup>

<sup>a</sup> Anesthesiology, Surgical Intensive Care and Pain Medicine Department, Faculty of Medicine, Tanta University, Tanta, Egypt.

## Authors' contributions

This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

## Article Information

DOI: 10.9734/JAMMR/2023/v35i185130

## Open Peer Review History:

This journal follows the Advanced Open Peer Review policy. Identity of the Reviewers, Editor(s) and additional Reviewers, peer review comments, different versions of the manuscript, comments of the editors, etc are available here: <https://www.sdiarticle5.com/review-history/102398>

Original Research Article

Received: 20/05/2023

Accepted: 06/07/2023

Published: 17/07/2023

## ABSTRACT

**Background:** Millions of individuals worldwide suffer from septic shock and sepsis each year, with fatalities reaching one in four and often higher. This work was conducted to evaluate the impact of Ascorbic acid, hydrocortisone, and thiamine treatment on the 28th day mortality rate and the

\*Corresponding author;

outcomes (changes in SOFA score, incidence of organ dysfunction, alterations in serum procalcitonin level, changes in serum lactate level and total dose of vasopressor therapy.

**Methods:** This prospective randomised controlled double-blinded work was performed on 80 individuals ranging in age from 18 to 65 years old and presented with sepsis who were diagnosed based on the SSC 2016 and The SSC Bundle 2018 Update. The participants were divided into two groups at random. Group I (placebo): The conventional approach was used to treat those who were in this group. The participants were given 50 ml of normal saline intravenously within 30 minutes, 5 ml intravenously within 6 hours, and 10 ml intravenously within 12 hours. Group II: the participants had standard sepsis treatment as well as a combination of ascorbic acid 1.5 gm diluted in 50 ml of normal saline IV within 30 minutes of 6 hours and thiamine 200 mg diluted in 10 ml of normal saline IV over a 12-hour period. If the admission term was shorter than 4 days, this combination treatment was provided until the time of release for a total of 4 days.

**Results:** No statistically substantial variation was existed among both groups as regard incidence of 28th day mortality and incidence of organ dysfunction. At day one, the comparison of the mean values of mean arterial pressure (MAP) and cardiac index was comparable between the two groups. At day 2,3 and 4, the mean values of MAP were greater in group II in contrast to group I while cardiac index was greater in group I compared to group II. The mean value ( $\pm$  SD) of the total dose of noradrenaline was  $824.1 \pm 296.8$  mg in group I, and  $591.9 \pm 343.2$  mg in group II, with statistically substantial variation among the two groups ( $P < 0.001$ )

**Conclusions:** The combined use of ascorbic acid, thiamine, and hydrocortisone has no impact on the 28th day mortality and organ dysfunction among individuals with septic shock and sepsis but has a good impact on haemodynamic parameters and inflammatory markers during the period of drug administration.

*Keywords: Ascorbic acid; thiamine; hydrocortisone; sepsis.*

## 1. INTRODUCTION

Sepsis is a possibly fatal organ damage carried on by an inadequately controlled host response to infection [1-3]. The category of sepsis known as septic shock is characterized by extremely severe cellular, circulatory, and metabolic deficiencies with a higher mortality risk than sepsis alone [1]. Millions of people worldwide suffer sepsis and septic shock each year, which can often result in death rates as high as one in four [4-6].

Since more than 20 years ago, it has been known that low blood and intracellular levels of vitamin C are present in severely sick patients [7,8] and in experimental models of sepsis, where a severe vitamin C deficiencies manifests [9] Patients with septic infections who are critically sick frequently having extremely poor or undetectable levels of serum vitamin C, leading to an acute scorbutic status [10]. Potent antioxidant vitamin C eliminates oxygen free radicals directly, replaces other cellular antioxidants like tocopherol and tetrahydrobiopterin, and is an important cofactor for enzymes containing iron and copper [11,12] Antioxidants which target the intra-mitochondrial environment may be essential in the therapy of sepsis as mitochondrial malfunction plays an crucial part in the progress of the diseases [13].

Thiamine is the basis for thiamine pyrophosphate (TPP), an important cofactor for many decarboxylases necessary for the Krebs cycle, the metabolism of glucose, and the synthesis of ATP [14]. Thiamine is essential for numerous enzymatic procedures that maintain brain function and inter-neuronal communication [15] Thiamine has anti-inflammatory effects and inhibits NF-B activation based on by oxidative stress [15] Thiamine deficiency affects septic patients frequently with prevalence rates varying between 20% and 70%, depending on the method of testing and inclusion criteria [16,17]. Neuronal cell death caused by excitotoxicity is correlated with thiamine deficiency. [18] In critically ill populations, thiamine deficiency may be related to higher mortality [19].

Several different glucocorticoids have anti-inflammatory effects. Almost all immune system cells get affected by glucocorticoids. Through a variety of methods that affect both innate and adaptive immune responses, glucocorticoids reduce inflammation. A huge amount of pro-inflammatory genes, that encode chemokines, cytokines, & inflammatory enzymes, are suppressed by glucocorticoids, which is their main anti-inflammatory effect. Low-dose glucocorticoids have immune-stimulating impacts along with attenuating the pro-inflammatory

reaction, which may limit the anti-inflammatory immunosuppressive state [20].

Mark et al. [10] who performed a wide interest retrospective study the utilization of hydrocortisone, thiamine, and ascorbic acid in sepsis individuals shows a substantial decrease in the mortality rate, created the need to perform prospective randomized controlled trials to investigate their results and to escalate the level of evidence.

In individuals with sepsis, we recommended that the usage of a combination of ascorbic acid, hydrocortisone, and thiamine could reduce fatality rates and improve outcomes.

The purpose of this work was to evaluate the impact of hydrocortisone, thiamine and ascorbic acid therapy on the mortality rate at 28 days in addition to other outcomes, including changes in SOFA score, incidence of organ dysfunction, alterations in serum procalcitonin level, changes in serum lactate level, and total dose of vasopressor therapy.

## 2. METHODS

During the 24-month period from November 2019 to October 2021, 80 patients from the Surgical Intensive Care Units (SICU) at Tanta University Hospitals who presented with sepsis and were diagnosed via the SSC 2016 [21] and The SSC Bundle 2018 Update [22] received this prospective randomised controlled double-blinded work. The participants' ages ranged from 18 to 65. The study gained approval from the Institutional Ethical Committee with the number (33375/09/19) then the study was registered on clinical trial.gov before first patient enrolment (ID NCT04160676). Each patient receives a secret code number and informed written agreement was collected from them or their families once they had been told of the study's aims.

Relatives of participants who refused to resume the study, suspected or known drug allergies, contraindications to vitamin C use due to renal stones, schizophrenia and Alzheimer's disease, prior organ malfunction or failure unrelated to the current sepsis situation, and pregnancy were all grounds for exclusion.

Participants in the research have to meet the inclusion requirements. With the use of computer-generated software for randomization that was placed inside sealed, unopened

envelopes, the patients were divided into two groups randomly. Placebo Group I: Only the SSC 2016 [21] and the SSC bundle 2018 update [22] were used to manage the patients in this group. The patients were given 50 ml of normal saline intravenously within 30 minutes, 5 ml intravenously within 6 hours, and 10 ml intravenously within 12 hours. Group II: The patients got hydrocortisone therapy in addition to standard sepsis treatment (Solucortif® 100 mg, dry powder, Pfizer, Egypt). Ascorbic acid (VITAMIN C-®, Amp, ROTEXMEDICA, Germany, 500mg/5ml), 50 mg diluted in 5 ml normal saline, IV / 6 h The combination of treatment was administered for 4 days or until the time of release if the admission duration was shorter than 4 days. Thiamine (Vitamin B1-injektipas®, Ampoule, Germany, 100 mg / 2 ml) and 1.5 gm were given intravenously within 30 minutes and six hours, respectively.

The preparation of the utilized drugs in syringes containing medications in group two and normal saline in group one was assisted by an intensivist who had no further part in this study work. The intensivist who prepared the drugs substitute normal saline for hydrocortisone if it had been recommended as a component of conventional treatment.

According to the SSC 2016 [21] and The SSC Bundle 2018 Update [22], all patients got the standard of care.

Doctors who were blind to the research groups and didn't take part in it gathered all the data.

The following procedures were applied to all of the patients: Collecting demographic data (gender, age, weight, and the cause of sepsis), estimating 28th-day mortality (if the participant was discharged, data were gathered by phone calls), recording SOFA score daily and comparing it throughout the administration of the studied drugs, recording the incidence of organ dysfunction throughout the ICU stay, recording mean arterial blood pressure (MAP) every eight hours and comparing it for four days, and measuring cardiac index every eight hours using an electrocardiogram.

### 2.1 Sample Size Calculation

Sample size was measured by using Open Epi Version 3.01. The calculated number was 37 patients per group, and increased to 40 patients per group after considering the drop out ratio

based on the following: Two-sided significance level 95%, power 90%, ratio of cases to control 1:1, and mortality rate was 40% among patients on the conventional management (placebo group) compared to 8.5% mortality rate among the group with the new intervention Ascorbic acid, hydrocortisone, and thiamine therapy [10].

### 2.2 Statistical Analysis

Version 20.0 of the IBM SPSS software program, available from IBM Corp. in Armonk, New York, was used for the statistical study. The student t-test was used to evaluate quantitative data that were provided as mean ± standard deviation. The Mann-Whitney test was used for evaluating non-normal distribution data that were reported as median and interquartile range. Chi Square tests were used to compare categorical data that were provided as frequency and percentage. The cut-off for statistical significance was  $p < 0.05$ .

### 3. RESULTS

No statistically substantial variation existed among the two groups as regard medical history, demographic characteristics, and cause of sepsis (Table 1).

No statistically substantial variation existed among the two groups as regard incidence of 28<sup>th</sup> day mortality and incidence of organ dysfunction (Table 2).

From day one up to day four, the follow up of SOFA scores were insignificantly different between both groups ( $P = 0.116, 0.193, 0.121,$  and  $0.142$  respectively) (Table 3).

At day one, the comparison of the mean values of MAP and cardiac index was comparable between the two groups. At day 2,3 and 4, the mean values of MAP were greater in group II as contrasted to group I while cardiac index was

**Table 1. Demographic characteristics, medical history and cause of sepsis of the studied group**

	Group I (n= 40)	Group II (n= 40)	P
<b>Age (years)</b>	45.53 ± 10.473	48.45 ± 9.886	0.203
Gender	Male	17 (42.5%)	0.501
	Female	23 (57.5%)	
Weight (kg)	87.53 ± 15.986	88.60 ± 13.994	0.750
Smoking	24 (60.0%)	22 (55.0%)	0.651
DM	18 (45.0%)	16 (40.0%)	0.651
HTN	13 (32.5%)	17 (42.5%)	0.356
IHD	10 (25.0%)	9 (22.5%)	0.793
Bronchial Asthma	5 (12.5%)	1 (2.5%)	0.090
<b>Cause of sepsis</b>			
Diabetic Foot	16 (40.0%)	14 (35.0%)	0.518
Fournier Gangrene	1 (2.5%)	2 (5.0%)	
Intestinal obstruction	13 (32.5%)	18 (45.0%)	
Chest infection	10 (25.0%)	6 (15.0%)	

DM: diabetes mellitus; HTN: hypertension; IHD: ischemic heart disease

**Table 2. Incidence of 28<sup>th</sup> day mortality, and organ dysfunction of the studied groups**

	Group I (n= 40)	Group II (n= 40)	Odds ratio	95% CI	P
28 <sup>th</sup> day Mortality	12 (30%)	9 (22.5%)	0.68	0.248,1.848	0.446
CNS	14 (35.0%)	8 (20.0%)	0.46	1.689,1.276	0.133
CVS	32 (80.0%)	34 (85.0%)	1.42	0.442,4.534	0.556
Respiration	14 (35.0%)	13 (32.5%)	0.89	0.353,2.260	0.813
Coagulopathy	5 (12.5%)	4 (10.0%)	0.78	0.192,3.137	0.723
Hepato-biliary	5 (12.5%)	3 (7.5%)	0.57	0.126,2.554	0.456
Renal	4 (10.0%)	3 (7.5%)	0.73	0.152,3.492	0.692
MODS	21 (52.5%)	18 (45%)	0.74	0.307,1.783	0.502

CI: confidence interval for mean difference; CVS: cardiovascular system; CNS: central nervous system; MODS: multi-organ damage

**Table 3. Baseline SOFA score on admission and its follow up during the current study in the studied groups**

SOFA	Group I (n= 40)	Group II (n= 40)	95% CI	P
Baseline	6.70 ± 2.04	5.93 ± 1.98	-0.1, 1.7	0.089
Day 1	6.10 ± 2.29	5.25 ± 2.49	-0.2, 1.9	0.116
Day 2	5.68 ± 2.36	4.90 ± 2.89	-0.4, 1.9	0.193
Day 3	5.20 ± 2.69	4.18 ± 3.14	-0.3, 2.3	0.121
Day 4	4.58 ± 3.05	3.55 ± 3.12	-0.3, 2.4	0.142

CI: confidence interval for mean difference

higher in group I contrasted to group II. The mean value (± SD) of the total dose of noradrenaline was 824.1 ± 296.8 mg in group I, and 591.9 ± 343.2 mg in group II, with statistically substantial variation among the two groups (P<0.001) (Table 4).

At day one, the mean values (± SD) of serum lactate were 14.70 ± 5.92 mmol/l in group I, and 13.27 ± 6.10 mmol/l in group II, with statistically insignificant variation among the two groups (P=

0.292). At day 2,3,4 the mean values were greater in group I in contrast to group II (P= 0.040, 0.048, 0.019 respectively). The median value (IQR) of the base line serum procalcitonin level was 24.45 (12.05, 31.43) ng/L in group I, and 23.15 (10.85, 31.88) ng/L in group II, with statistically insignificant variation among the two groups (P=0.715). At the 4th day, the median value (IQR) of serum procalcitonin level was lower in group II, as contrasted to group I. (P= 0.044) (Table 5).

**Table 4. Baseline MAP (mmHg), and cardiac index on admission and its follow up during the current study, and total noradrenaline dose in the studied group**

MAP (mmHg)	Group I (n= 40)	Group II (n= 40)	P
<b>Baseline</b>	66.78 ± 7.36	65.58 ± 6.79	0.451
<b>Day 1</b>			
8h	67.00 ± 7.55	67.75 ± 7.99	0.667
16h	67.30 ± 7.67	68.13 ± 8.04	0.640
24h	67.50 ± 7.98	68.47 ± 8.47	0.598
<b>Day 2</b>			
8h	67.80 ± 8.22	72.85 ± 9.35	0.012*
16h	67.95 ± 8.55	73.40 ± 9.21	0.008*
24h	68.18 ± 8.97	74.00 ± 9.13	0.005*
<b>Day 3</b>			
8h	68.33 ± 9.39	74.55 ± 9.93	0.005*
16h	68.50 ± 9.42	74.43 ± 9.73	0.007*
24h	68.55 ± 9.67	74.22 ± 9.98	0.012*
<b>Day 4</b>			
8h	68.72 ± 9.82	74.10 ± 10.43	0.020*
16h	68.88 ± 10.36	74.15 ± 11.06	0.031*
24h	68.97 ± 10.83	74.20 ± 12.13	0.045*
<b>Cardiac index</b>			
<b>Baseline</b>	3.81 ± 0.412	3.87 ± 0.37	0.472
<b>Day 1</b>			
8h	3.74 ± 0.42	3.68 ± 0.45	0.561
16h	3.72 ± 0.42	3.70 ± 0.44	0.822
24h	3.70 ± 0.43	3.71 ± 0.47	0.894
<b>Day 2</b>			
8h	3.67 ± 0.43	3.42 ± 0.52	0.023*
16h	3.66 ± 0.45	3.39 ± 0.49	0.013*
24h	3.65 ± 0.47	3.37 ± 0.48	0.009*
<b>Day 3</b>			
8h	3.64 ± 0.49	3.34 ± 0.48	0.008*
16h	3.63 ± 0.51	3.33 ± 0.50	0.009*
24h	3.61 ± 0.53	3.31 ± 0.56	0.015*
<b>Day 4</b>			
8h	3.60 ± 0.56	3.30 ± 0.64	0.026*
16h	3.56 ± 0.58	3.28 ± 0.64	0.041*
24h	3.59 ± 0.59	3.30 ± 0.63	0.038*
Noradrenaline total dose (mg)	824.1±296.8	591.9 ± 343.2	< 0.001*

\*Indicates substantial variation among two groups (p<0.05)

**Table 5. Baseline serum Lactate (mmol/L), and procalcitonin (ng/L) on admission and its follow up during the current study in the studied groups**

Lactate	Group I (n= 40)	Group II (n= 40)	P
Baseline	15.04 ± 5.59	14.92 ± 6.25	0.928
Day 1	14.70 ± 5.92	13.27 ± 6.25	0.292
Day 2	14.65 ± 6.71	11.72 ± 5.81	0.040*
Day 3	14.57 ± 7.76	11.37 ± 5.81	0.048*
Day 4	14.63 ± 8.68	10.51 ± 6.62	0.019*
<b>Procalcitonin</b>			
Baseline	24.45 (12.05, 31.43)	23.15 (10.85, 31.88)	0.715
End of study	11.25 (4.10, 25.38)	7.40 (3.73, 12.98)	0.044*

#### 4. DISCUSSION

For those having septic shock and sepsis, the combined administration of thiamine, ascorbic acid, and hydrocortisone has shown promise as an adjuvant treatment to antibiotics, the management of infectious sources, and supportive care. It is believed that these three medications complement one another and minimize organ dysfunction, mortality, and the amount of time spent on vasopressors.

Our study's findings showed that the incidence of 28<sup>th</sup> day mortality, the incidence of organ dysfunction and SOFA score follow up throughout the period of the study were insignificantly different between both groups. The MAP was higher, with lower cardiac index, serum procalcitonin, serum lactate and total dose of vasopressor drug in group II.

Chang et al. [23] assessed the safety and effectiveness of the combined use of hydrocortisone, vitamin C, and thiamine for septic shock and sepsis in a randomized, controlled experiment on 80 individuals and demonstrated that no variations was existed in 28-day mortality among both groups, which is consistent with our study.

Using 1427 patients, Weilan et al [24] performed a meta-analysis to assess the impact of a combined use of ascorbic acid, hydrocortisone, and thiamine on those suffering from sepsis and septic shock. They didn't see any appreciable reduction in hospital mortality.

The usage of ascorbic acid, hydrocortisone, and thiamine therapy in septic shock and sepsis was also studied by Ragoonanan et al [25] in a meta-analyses, however they discovered no indication that mortality was improved.

In addition, Iglesias et al. [26] evaluated the combination of IV ascorbic acid,

hydrocortisone, and thiamine therapy bundle for the treatment of septic shock and sepsis individuals admitted to ICU but observed no improvement in the mortality rate or SOFA score in their randomised placebo-controlled double-blinded study of 137 patients.

In a multi-center, double-blinded, randomised, controlled research, Hwang et al [27] assessed the impact of early combined use of vitamin C and thiamine on rehabilitation from organ dysfunction among individuals with septic shock. Between the therapy group and the placebo group, there was no discernible change in 28-day mortality and SOFA scores with no improvement in organ failure versus ascertain if the combination of corticosteroids, ascorbic acid, and thiamine attenuates organ harm in individuals with septic shock, Moskowitz et al [28] conducted a randomized, blinded, multi-center clinical study comparing corticosteroids, ascorbic acid, and thiamine versus placebo. They came to the conclusion that, in contrast to a placebo, the combined use of corticosteroids, ascorbic acid, and thiamine did not result in a statistically substantial decrease in SOFA score throughout the first 72 hours of enrolment or a decrease in 30-day mortality.

According to Vail et al. [29], receiving corticosteroids, ascorbic acid, and thiamine was not linked to a reduction in mortality among those suffering from early septic shock.

Additionally, in a retrospective cohort trial, Litwak et al [30] examined the mortality advantages of triple treatment, which combines hydrocortisone, vitamin C, and thiamine, in along with normal care, for individuals with serious septic shock and sepsis. They came to the conclusion that administering a combined IV medication of thiamine, hydrocortisone, and vitamin C had no effect on hospital mortality.

Additionally, neither the 28-day mortality nor the ICU or hospital mortality among the two groups were significantly different, according to Lyu et al. [31]

Marik et al. [10] on the other hand, conducted retrospective research to compare the results and clinical course of those with septic receiving intravenous hydrocortisone, vitamin C, and thiamine over a 7-month period (treatment group) with a control group managed throughout the 7-month period before (control group). According to their findings, the early administration of intravenous vitamin C, alongside corticosteroids and thiamine, was successful in halting the progression of organ failure, including acute kidney damage, and in lowering the mortality among individuals with serious septic shock and sepsis.

Additionally, Song et al [32] investigated the efficacy of combining vitamin C, thiamine, and hydrocortisone in the treatment of sepsis. They noted that the ascorbic acid, hydrocortisone, and thiamine regimen had a positive impact on the SOFA score and reduced the death rate of those suffering from septic shock and sepsis.

Additionally, Kim et al [33] assessed the effectiveness of treating individuals who had severe pneumonia with a combination of hydrocortisone, vitamin C, and thiamine. We compared the group of individuals with severe pneumonia who received treatment with ascorbic acid, hydrocortisone, and thiamine (n = 53) to the group of individuals with severe pneumonia who received standard care (n = 46). The combination of thiamine, hydrocortisone, and vitamin C treatment independently lowered mortality.

Additionally, Coloretti et al. [34] conducted a retrospective analysis to determine if triple treatment, which combines hydrocortisone, vitamin C, and thiamine, might enhance results for individuals with refractory shock compared with steroids alone. The triple therapy appeared to enhance clinical results for individuals with refractory septic shock as evidenced by the shorter duration of mechanical ventilation and a tendency to lower 30-day and death rates in hospitals when contrasted with single therapy using only hydrocortisone.

Additionally, Wald et al. [35] investigated the possibility that thiamine, ascorbic acid, and hydrocortisone might reduce mortality in children

with septic shock. They discovered that compared to matched controls and matched hydrocortisone alone patients, those who got ascorbic acid-hydrocortisone-thiamine treatment had substantially decreased 30-day mortality.

Additionally, in a retrospective cohort research, Sadaka et al. [36] investigated the use of thiamine, ascorbic acid, and steroids in septic shock. In comparison to the placebo group, they found decreased hospital mortality and a tendency toward lower ICU mortality.

According to the three medications' mechanisms of action, they should complement one another and lessen the endothelial barrier alterations brought on by septic shock as well as avoid nephropathy brought on by an excess of oxalates [30].

Our result revealed that, the combination therapy of ascorbic acid, hydrocortisone, and thiamine was associated with higher MAP and lower dose of vasopressor drug as compared to the conventional therapy.

In line with our findings Weilan et al. [24] showed that the duration of vasopressor therapy was reduced with the combination therapy.

Also, Ragoonanan et a. [25] documented that the hemodynamic benefit was most pronounced when ascorbic acid, hydrocortisone, thiamine therapy was initiated early in the disease course.

Moreover, Song et al. [32] reported that reduction in usage of vasopressor agents with the combination therapy in treating sepsis.

In contrast to our results, Hwang et al. [27], Litwak et al [30], Lyu et al [31], Fujii et al[37], and Wald et al [35] reported that the addition of the combined use of hydrocortisone, ascorbic acid, thiamine in treating sepsis did not provide reduction of the vasopressor usage.

Our results revealed that, the combination of ascorbic acid, hydrocortisone, and thiamine was associated with lower serum lactate and procalcitonin levels as compared to the conventional therapy.

Weilan et al [24], Marik et al [10], and Wald et al [35] they documented that the addition of the combined use of ascorbic acid, thiamine and hydrocortisone was correlated with decreased level of serum lactate and procalcitonin.

In contrast, Chang et al [23], Iglesias et al [26], Hwang et al [27], and Litwak et al [30] found that the combination therapy had no improvement on serum lactate and levels of procalcitonin among individuals with septic shock and sepsis.

Our research has certain drawbacks. It is unclear whether those randomized had thiamine hypovitaminosis at randomization and whether such hypovitaminosis was rectified or not because the study was conducted in a single center and the potential individual impacts of thiamine and vitamin C were not evaluated on its own. Further assessment of ascorbic acid, thiamine and hydrocortisone therapy is needed via wide scale multi-centre study to overcome the variety of vitamin C regimens employed, as well as the timing and length of therapy.

## 5. CONCLUSIONS

In patients with septic shock and sepsis, the combined use of thiamine, ascorbic acid, and hydrocortisone had little impact on organ failure and 28th day mortality but has a good impact on haemodynamic parameters and inflammatory markers during the period of drug administration.

## ETHICAL APPROVAL AND CONSENT

The study gained approval from the Institutional Ethical Committee with the number (33375/09/19) then the study was registered on clinical trial.gov before first patient enrolment (ID NCT04160676). Each patient receives a secret code number and informed written agreement was collected from them or their families once they had been told of the study's aims.

## COMPETING INTERESTS

Authors have declared that no competing interests exist.

## REFERENCES

1. Singer M, Deutschman CS, Seymour CW, Shankar-Hari M, Annane D, Bauer M, et al. The third international consensus definitions for sepsis and septic shock (Sepsis-3). *Journal of the American Medical Association*. 2016;315:801-10.
2. Shankar-Hari M, Phillips GS, Levy ML, Seymour CW, Liu VX, Deutschman CS, et al. Developing a new definition and

assessing new clinical criteria for septic shock: For the third international consensus definitions for sepsis and septic shock (Sepsis-3). *Journal of the American Medical Association*. 2016;315:775-87.

3. Seymour CW, Liu VX, Iwashyna TJ, Brunkhorst FM, Rea TD, Scherag A, et al. Assessment of clinical criteria for sepsis: for the third international consensus definitions for sepsis and septic shock (Sepsis-3). *Journal of the American Medical Association*. 2016;315:762-74.
4. Angus DC, Linde-Zwirble WT, Lidicker J, Clermont G, Carcillo J, Pinsky MR. Epidemiology of severe sepsis in the United States: Analysis of incidence, outcome, and associated costs of care. *Critical Care Medicine*. 2001;29:1303-10.
5. Dellinger RP. Cardiovascular management of septic shock. *Critical Care Medicine*. 2003;31:946-55.
6. Martin GS, Mannino DM, Eaton S, Moss M. The epidemiology of sepsis in the United States from 1979 through 2000. *The New England Journal of Medicine*. 2003;348:1546-54.
7. Galley HF, Davies MJ, Webster NR. Ascorbyl radical formation in patients with sepsis: Effect of ascorbate loading. *Free Radical Biology and Medicine*. 1996;20:139-43.
8. Borrelli E, Roux-Lombard P, Grau GE, Girardin E, Ricou B, Dayer J-M, et al. Plasma concentrations of cytokines, their soluble receptors, and antioxidant vitamins can predict the development of multiple organ failure in patients at risk. *Critical Care Medicine*. 1996;24:392-7.
9. Armour J, Tymk K, Lidington D, Wilson JX. Ascorbate prevents microvascular dysfunction in the skeletal muscle of the septic rat. *Journal of Applied Physiology*. 2001;90:795-803.
10. Marik PE, Khangoora V, Rivera R, Hooper MH, Catravas J. Hydrocortisone, Vitamin C, and Thiamine for the Treatment of Severe Sepsis and Septic Shock: A Retrospective Before-After Study. *Chest*. 2017;151:1229-38.
11. May JM, Harrison FE. Role of vitamin C in the function of the vascular endothelium. *Antioxidants and Redox Signaling*. 2013;19:2068-83.
12. Wilson JX. Evaluation of vitamin C for adjuvant sepsis therapy. *Antioxidants and Redox Signaling*. 2013;19:2129-40.



13. Kc S, Cárcamo JM, Golde DW. Vitamin C enters mitochondria via facilitative glucose transporter 1 (Glut1) and confers mitochondrial protection against oxidative injury. *FASEB Bioadvances*. 2005;19:1657-67.
14. Collie JT, Greaves RF, Jones OA, Lam Q, Eastwood GM, Bellomo R. Vitamin B1 in critically ill patients: Needs and challenges. *Clinical Chemistry and Laboratory Medicine*. 2017;55:1652-68.
15. Manzetti S, Zhang J, van der Spoel D. Thiamin function, metabolism, uptake, and transport. *Biochemistry*. 2014;53:821-35.
16. Wesselink E, Koekkoek W, Grefte S, Witkamp R, van Zanten A. Feeding mitochondria: potential role of nutritional components to improve critical illness convalescence. *Clinical Nutrition* 2018; 38:982-95.
17. Donnino MW, Carney E, Cocchi MN, Barbash I, Chase M, Joyce N, et al. Thiamine deficiency in critically ill patients with sepsis. *The Journal of Critical Care*. 2010;25:576-81.
18. Hazell AS, Faim S, Wertheimer G, Silva VR, Marques CS. The impact of oxidative stress in thiamine deficiency: A multifactorial targeting issue. *Neurochem Int*. 2013;62:796-802.
19. Jensen GL, Wheeler D. A new approach to defining and diagnosing malnutrition in adult critical illness. *Current Opinion in Critical Care*. 2012;18:206-11.
20. Keh D, Boehnke T, Weber-Cartens S, Schulz C, Ahlers O, Bercker S, et al. Immunologic and hemodynamic effects of "low-dose" hydrocortisone in septic shock: a double-blind, randomized, placebo-controlled, crossover study. *American Journal of Respiratory and Critical Care Medicine*. 2003;167:512-20.
21. Rhodes A, Evans LE, Alhazzani W, Levy MM, Antonelli M, Ferrer R, et al. Surviving sepsis campaign: international guidelines for management of sepsis and septic shock: 2016. *Intensive Care Medicine*. 2017;43:304-77.
22. Levy MM, Evans LE, Rhodes A. The surviving sepsis campaign bundle: 2018 update. *Intensive Care Med*. 2018;44:925-8.
23. Chang P, Liao Y, Guan J, Guo Y, Zhao M, Hu J, et al. Combined treatment with hydrocortisone, vitamin C, and thiamine for sepsis and septic shock: a randomized controlled trial. *Chest*. 2020;158:174-82.
24. Na W, Shen H, Li Y, Qu D. Hydrocortisone, ascorbic acid, and thiamine (HAT) for sepsis and septic shock: a meta-analysis with sequential trial analysis. *Journal of Intensive Care*. 2021;9:1-13.
25. Ragoonanan D, Tran N, Modi V, Morgan Nickelsen P. Unanswered questions on the use of hydrocortisone, ascorbic acid, and thiamine therapy in sepsis and septic shock. *American Journal of Health-System Pharmacy*. 2022;79:1626-33.
26. Iglesias J, Vassallo AV, Patel VV, Sullivan JB, Cavanaugh J, Elbaga Y. Outcomes of metabolic resuscitation using ascorbic acid, thiamine, and glucocorticoids in the early treatment of sepsis: the ORANGES trial. *Chest*. 2020;158:164-73.
27. Hwang SY, Ryoo SM, Park JE, Jo YH, Jang D-H, Suh GJ, et al. Combination therapy of vitamin C and thiamine for septic shock: a multi-centre, double-blinded randomized, controlled study. *Intensive Care Medicine*. 2020;46:2015-25.
28. Moskowitz A, Huang DT, Hou PC, Gong J, Doshi PB, Grossestreuer AV, et al. Effect of ascorbic acid, corticosteroids, and thiamine on organ injury in septic shock: The ACTS randomized clinical trial. *Journal of the American Medical Association*. 2020;324:642-50.
29. Vail EA, Wunsch H, Pinto R, Bosch NA, Walkey AJ, Lindenauer PK, et al. Use of hydrocortisone, ascorbic acid, and thiamine in adults with septic shock. *American Journal of Respiratory and Critical Care Medicine*. 2020;202:1531-9.
30. Litwak JJ, Cho N, Nguyen HB, Moussavi K, Bushell T. Vitamin C, hydrocortisone, and thiamine for the treatment of severe sepsis and septic shock: a retrospective analysis of real-world application. *Journal of Clinical Medicine*. 2019;8:478.
31. Lyu Q-Q, Zheng R-Q, Chen Q-H, Yu J-Q, Shao J, Gu X-H. Early administration of hydrocortisone, vitamin C, and thiamine in adult patients with septic shock: a randomized controlled clinical trial. *Critical Care*. 2022;26:1-11.
32. Song W, Wu J. The controversy and value of the combination of hydrocortisone, ascorbic acid and thiamine in treating sepsis. *Zhonghua Yi Xue Za Zhi*. 2021;101:1206-9.
33. Kim W-Y, Jo E-J, Eom JS, Mok J, Kim M-H, Kim KU, et al. Combined vitamin C,

- hydrocortisone, and thiamine therapy for patients with severe pneumonia who were admitted to the intensive care unit: Propensity score-based analysis of a before-after cohort study. *Journal of Critical Care*. 2018;47:211-8.
34. Coloretti I, Biagioni E, Venturelli S, Munari E, Tosi M, Roat E, et al. Adjunctive therapy with vitamin c and thiamine in patients treated with steroids for refractory septic shock: A propensity matched before-after, case-control study. *Journal of Critical Care*. 2020;59:37-41.
35. Wald EL, Sanchez-Pinto LN, Smith CM, Moran T, Badke CM, Barhight MF, et al. Hydrocortisone–ascorbic acid–thiamine use associated with lower mortality in pediatric septic shock. *American Journal of Respiratory and Critical Care Medicine*. 2020;201:863-7.
36. Sadaka F, Grady J, Organti N, Donepudi B, Korobey M, Tannehill D, et al. Ascorbic acid, thiamine, and steroids in septic shock: Propensity matched analysis. *Journal of Intensive Care Medicine*. 2020;35:1302-6.
37. Fujii T, Luethi N, Young PJ, Frei DR, Eastwood GM, French CJ, et al. Effect of vitamin C, hydrocortisone, and thiamine vs hydrocortisone alone on time alive and free of vasopressor support among patients with septic shock: The vitamins randomized clinical trial. *Journal of the American Medical Association*. 2020;323:423-31.

© 2023 Sharaf et al.; This is an Open Access article distributed under the terms of the Creative Commons Attribution License (<http://creativecommons.org/licenses/by/4.0>), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

*Peer-review history:*  
*The peer review history for this paper can be accessed here:*  
<https://www.sdiarticle5.com/review-history/102398>