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Systematic Review on Impacts of Vitamin C, Thiamin, and Hydrocortisone in Sepsis

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Abstract
Sepsis is one of the most common conditions causing prolonged hospitalizations. Sepsis is a systemic infectious process that can be caused by multiple sources and types of infection in the human body. In developing and developed countries, sepsis is a condition that can put a financial burden on the health system due to longer stays in the hospital and the need for mechanical ventilators and vasopressors. Also, sepsis has a higher rate of mortality and morbidity for patients in lower-income countries due to lower levels of symptom awareness, health inequity, delay in care, and under-resourced healthcare facilities. Healthcare professionals are interested in finding evidence-based approaches to decrease mortality and morbidity and reduce the financial burden on an already stressed health system. This systematic article review aims to appraise articles using a hierarchy of evidence to address the clinical question regarding the efficacy of vitamin C, steroids, and thiamine in sepsis and septic patients when added to the standard treatment. After reviewing the randomized control trial, we found that study results on the regular use of vitamin C, steroids, and thiamine in sepsis and septic shock are conflicting. More research is needed to assess the efficacy of vitamin C, steroids, and thiamine in sepsis and septic shock to improve patient outcomes and reduce the length of hospitalizations.

Keywords: Vitamin C, Steroids, Thiamine, Sepsis, and Septic shock

1. Introduction

Sepsis is one of the most common causes of prolonged hospitalization for patients seen in healthcare facilities. According to Rudd et al. (2020), sepsis caused around 11 million deaths in 2017 worldwide, which accounted for around 19.7% of global deaths. This number might underestimate the burden of sepsis globally because data collection on the incidence is poorly collected in lower- and middle-income countries. In many countries, access to healthcare services is limited and health records are only partially complete (Dugani et al., 2017). Globally, around 30 million sepsis cases occur yearly, leading to more than 8 million deaths, where 40-50% occur in lower-income countries (Cohen et al., 2015; Fleischmann et al., 2016).

The data on the burden of sepsis in lower-income countries is limited due to incomplete medical charts and the lack of incorporation of the International Classification Diseases Code system (Dugani et al., 2017). However, in

the United States, about 55% of patients diagnosed with sepsis need care management at the intensive care unit level, with a death rate of 20% to 30% (Rhee et al., 2017). According to Rhee et al. (2017), in the United States, sepsis ranks as the third leading cause of healthcare facility death. The patient population who survives sepsis is often at risk of experiencing poor physical and mental or cognitive outcomes and a suboptimal quality of life (Yende et al., 2016). It is difficult to estimate the financial burden of sepsis globally. Van den Berg et al. (2017) in a systematic review assessed the hospital-related financial burden of sepsis around the world and found that the relative amount of healthcare budget spent on sepsis was 2.65% which is 0.33% of the gross national product. In the United States, sepsis costs $38 billion annually (Hollenbeck et al., 2023).

Sepsis is an infectious condition that can lead to high mortality and morbidity rates (Rudd et al., 2020), but does not have a current universal definition. From 1991 to 2016, multiple definitions have been suggested. In 2016, sepsis was generally defined as a life-threatening condition with organ dysfunction as the body's response to infectious processes (Singer et al., 2016).

Sepsis has higher mortality and morbidity rates than other conditions requiring prolonged hospitalization, with a substantial financial burden on the health system in lower and higher-income countries. In lower-income countries health inequity, limited financial resources, health disparity, corruption, suboptimal healthcare services, and resilient public health are the main contributors to the sepsis burden (Rudd et al., 2018).

The definition of sepsis was developed in 1991 at a consensus conference that linked infection with the systemic inflammatory response (Bone et al., 1992); (See **Table 1** illustrating sepsis criteria). According to Chakraborty & Burns (2023), systemic inflammatory response syndrome (SIRS) is the human body's response to internal and external toxic or stressor stimuli such as infection, trauma, surgery, burn, or malignancy. SIRS in the adult population is objectively defined by the presence of two criteria (body temperature more than 38 or less than 36 degrees Celsius, heart rate more than 90/minute, respiratory rate more than 20/minute, and white blood count more than 12000 or less than 4000/microliters or the presence of bandemia at greater than 10% band cells). Kaukonen et al. (2015) added to the theory that almost all septic patients meet SIRS criteria. However, all patients with SIRS criteria are not septic.

It is essential to highlight the subgroups of patients who might not meet SIRS criteria when they present to the healthcare facility, specifically the old patient population. The older patient population can develop multi-organ failure and severe forms of infections and death (Kaukonen et al., 2015). It can be difficult for the local provider to diagnose older patients from either SIRS or classical forms of sepsis.

This debate between a clear definition of SIRS and a more detailed definition of sepsis led the European Society of Intensive Critical Medicine (SCCM) to create a new task force that developed Sepsis-3, a new definition of sepsis (Fernando et al., 2018). According to Fernando et al. (2018), the new definition entailed any life-threatening organ dysfunction due to the body's dysregulated response to infection. The new definition for the diagnosis of sepsis does not entail SIRS criteria to establish a delineation between symptoms to define the diagnosis further.
Currently, the Sequential Organ Failure Assessment (SOFA) scores are used as a vital criterion in the diagnosis of a patient with sepsis (Singer et al., 2016). According to Vincent et al. (1996), SOFA scores are based on assessing six systems: respiratory, cardiovascular, liver function, coagulation profile, kidney function, and nervous system. Each system is scored 0 to 4 (Vincent et al. 1996). (See **Table 2** illustrating SOFA criteria). According to Chakraborty & Burns (2023), besides SOFA, several scoring systems are used to assess organ dysfunction, such as the Acute Physiology and Chronic Health Evaluation (APACH) score II and III, Multiple Organ Dysfunction (MOD) score, and Logistic Organ Dysfunction (LOD) score.

To date, the medical measures that have enhanced outcomes for sepsis patients are early initiation of antibiotics, fluid resuscitation, and other appropriate interventions to control or address the source of infection (Rhodes et al., 2017). Different measures are suggested to help manage sepsis, including administering intravenous Vitamin C, hydrocortisone, and thiamin in observational studies based on biological plausibility (Merik et al., 2017; Wilson, 2013). The need exists for a universal definition of sepsis to support the review of potential interventions to address this health condition. The purpose of this systematic is to assess the effects of vitamin C, thiamine, and

hydrocortisone in sepsis patients to determine if they have any significant impact on patients' early discharge from the hospital, ventilator free time, vasopressor-free time, mortality, in randomized controlled trials.

Table 1: Definitions of Sepsis

Bone et al. (1992)	Levy et al. (2003)	Singer et al. (2016)
Sepsis: Infection with two or SIRS criteria Severe Sepsis: Sepsis with organ dysfunction Septic shock: Hypotension with sepsis despite adequate fluid resuscitation along with indicators of abnormal perfusion: lactic acidosis, oliguria, altered mental status	Suspected or confirmed sources of infection with follow some of the following parameters **General Indicators:** Fever (core temperature > 38.3°C); hypothermia (core temperature < 36°C); heart rate > 90 beats per min or > 2 SD above the normal value for age; tachypnea: respiratory rate > 30 breaths per min; altered mental status; significant edema or positive fluid balance (>20 mL kg over 24 h) Hyperglycemia (plasma glucose > 110 mg dL) in the absence of diabetes **Inflammatory Indicators:** Leukocytosis (white blood cell count > 12,000/μL); leukopenia (white blood cell count < 4000/μL); normal white blood cell count with > 10% immature forms; plasma C-reactive protein > 2 SD above the normal value; and plasma procalcitonin > 2 SD above the normal value **Hemodynamic Indicator:** Hypotension (systolic blood pressure < 90 mmHg, MAP < 70 mmHg, or a systolic blood pressure decrease > 40 mmHg in adults or < 2 SD below normal for age, mixed venous oxygen saturation > 70%, cardiac index > 3.5 L min^{-1} m^{-2}) Organ dysfunction parameters: Arterial hypoxemia (PaO_2/FIO_2 < 300); acute oliguria (urine output < 0.5 mL/kg/ h); creatinine increase ⩾ 0.5 mg/ dL; coagulation abnormalities (international normalized ratio > 1.5 or activated partial thromboplastin time > 60 s); ileus; thrombocytopenia (platelet count < 100,000 μL) Hyperbilirubinemia (plasma total bilirubin > 4 mg/dL) **Tissue perfusion Indicator:** Hyperlactatemia (>3 mmol L^{-1}); decreased capillary refill or mottling	Sepsis is a life-threatening organ dysfunction caused by dysregulated host response to infection. **Sepsis criteria** Suspected or documented infection and presence of ⩾2 SOFA points Septic shock is defined presence of sepsis with persisting hypotension, Requiring vasopressor therapy to elevate MAP ⩾ 65 mmHg Lactate > 2 mmol L (18 mg/dL) despite adequate fluid resuscitation

Source: Gyawali, B., Ramakrishna, K., & Dhamoon, A. S. (2019). Sepsis: The evolution in definition, pathophysiology, and management. SAGE open medicine, 7, 2050312119835043. https://doi.org/10.1177/2050312119835043.

Table 2: SOFA Criteria

Respiratory system		
PaO2/FiO2 (mmHg)	SOFA score	
> 400		0
< 400		1
< 300		2
< 200 with respiratory support		3
< 100 with respiratory support		4
Nervous system		
Glasgow Coma Scale	SOFA score	
15		0
13–14		1
10–12		2
6–9		3
< 6		4
Cardiovascular system		
Mean arterial pressure (MAP) OR administration of vasopressors required	SOFA score	
MAP > 70 mmHg		0
MAP < 70 mm/Hg		1
Dopamine ≤ 5 µg/kg/min or dobutamine (any dose)		2
Dopamine > 5 µg/kg/min OR epinephrine ≤ 0.1 µg/kg/min OR norepinephrine ≤ 0.1 µg/kg/min		3
Dopamine > 15 µh/kg/min OR epinephrine > 0.1 µg/kg/min OR norepinephrine > 0.1 µg/kg/min		4
Liver		
Bilirubin (mg/dl) [µmol/L]	SOFA score	
< 1.2 (< 20)		0
1.2–1.9 [20–32]		1
2.0–5.9 [33–101]		2
6.0–11.9 [102–204]		3
> 12.0 [> 204]		4
Coagulation		
Platelets ×103/ml	SOFA score	
> 150		0
< 150		1
< 100		2
< 50		3
< 20		4
Kidneys		
Creatinine (mg/dl) [µmol/L]; urine output	SOFA score	
< 1.2 [< 110]		0
1.2–1.9 [110–170]		1
2.0–3.4 [171–299]		2
3.5–4.9 [300–440] (or urine output < 500 ml/day)		3
> 5.0 [> 440]; urine output < 200 ml/day		4

Source: Vincent, J. L., Moreno, R., Takala, J., Willatts, S., De Mendonça, A., Bruining, H., Reinhart, C. K., Suter, P. M., & Thijs, L. G. (1996). The SOFA (Sepsis-related Organ Failure Assessment) score to describe organ dysfunction/failure. On behalf of the Working Group on Sepsis-Related Problems of the European Society of Intensive Care Medicine. Intensive care medicine, 22(7), 707–710. https://doi.org/10.1007/BF01709751.

1.1. Etiology of Sepsis

According to Mahapatra & Heffner (2023), the 2009 European Prevalence of Infection in Intensive Care (EPIC II study) indicated that one of the most common etiology of sepsis is gram-negative bacterial infections. Gram-

negative bacterial infections account for 62% of the cases, followed by gram-positive infection, which accounts for 47% (Vincent et al., 2009). Study results determined causative bacterial organisms in septic patients as *Staphylococcus aureus* (20%), *Pseudomonas* (20%), and *Escherichia coli* (16%) (Vincent et al., 2009). Site-specific infections are commonly respiratory (42%), bloodstream (21%), and genitourinary (10%) (Mayr et al., 2010). Mahapatra & Heffner (2023) highlighted that diabetes, trauma, chronic liver disease, chronic kidney disease, immunocompromised state, burns, hemodialysis, indwelling catheters, major surgery, older age, and chronic use of steroids are considered the risk factors that can predispose to sepsis.

1.2. Sepsis Epidemiology

Cases of sepsis have increased in the last decades. In the United States, around 600,000 to 1,000,000 patients were hospitalized for sepsis per year from 2000 through 2008 (Elixhause et al., 2011). Mortality from sepsis can vary from country to country due to specific demographics such as age, sex, race, the existence of comorbid conditions, and organ failure (Mahapatra & Heffner, 2023). Elfeky et al. (2017) indicated that mortality associated with sepsis depends on the number and degree of organ failure, with crucial predictors being respiratory, hepatic, cardiovascular, and neurologic failure.

2. Search Strategy

We used PubMed.gov and Cochrane Library databases for articles on the effects of vitamin C, steroids, and thiamine in sepsis and septic shock patients. We included randomized control trials published within the last five years and excluded studies published prior to 2018 and those not written in English. Also, we excluded studies that investigated the vitamin C, steroids, and thiamine individually. We reviewed the abstracts of articles based on inclusion/exclusion criteria. In the first stage, we identified potentially 141 relevant articles. During the screening stage, we noticed that eight articles were duplicates. Moreover, during the screening process, we applied the inclusion criteria: (1) articles on the role of intravenous vitamin C, steroids, and thiamine in sepsis and septic shock patients, (2) participants of the study 18 years old or older, (3) articles that were published within the last five years in English, and (4) randomized controlled trials. In the eligibility phase, we excluded articles that were randomized clinical trials in which vitamin C, thiamine, and hydrocortisone were investigated individually. We found that 8 articles were eligible and included in our review. The literature selection process is described in the PRISMA diagram (Moher et al., 2015); (See **Figure 1** illustrating selection flow diagram**)**.

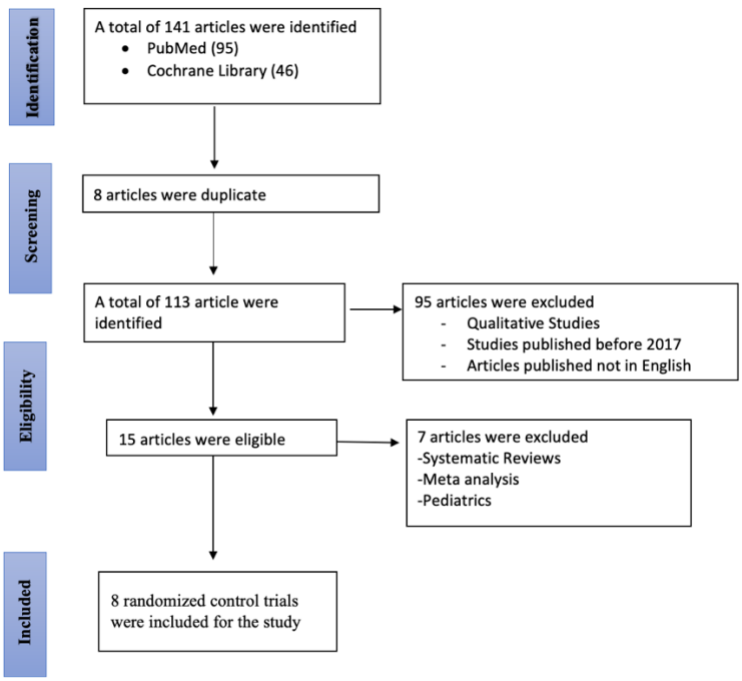

Figure 1: Selection Flow Diagram

2.1. Articles Quality Grading

We used the Oxford Center for Evidence-Based Medicine (Burn et al., 2011) scale to grade the quality of articles and included Level-1 evidence randomized control trials in our review; (see **Table 3** illustrating level of evidence and type of evidence) **.**

Table 3: Level and Type of Evidence

Type of evidence	**Level of evidence**	**Number of Articles**
All articles	L1, L2, L3, and L4	113
Randomized control trial	L1	8
Systematic Review, Meta analysis, and Pediatrics	L1	7
Other studies	L2, L3, and L4	95

Source: Burns, P. B., Rohrich, R. J., & Chung, K. C. (2011). The levels of evidence and their role in evidence-based medicine. Plastic and reconstructive surgery, 128(1), 305–310. https://doi.org/10.1097/PRS.0b013e318219c171.

3. Role of the Ascorbic Acid, Hydrocortisone, and Thiamine in Sepsis Patients on Ventilator and Vasopressor

3.1. Study Design

Sevransky et al. (2021) designed a randomized, double-masked study with an adaptive sample in adult patients with respiratory and circulatory failure needing vasopressors due to sepsis. Participants from 43 healthcare facilities were enrolled in the study in the United States. Participants were randomly assigned 1:1 to intervention and placebo groups.

3.2. Trial Participants

Participants aged 18 and older with respiratory and cardiovascular failure secondary to sepsis were enrolled in the study. Criteria for respiratory failure were arterial partial pressure ratio to the fraction of inspired oxygen ≥300 or blood oxygen saturation ratio to fraction inspired oxygen (FiO2) ≥315 and on the ventilator, and patients on noninvasive positive pressure ventilation, or oxygen with high-flow nasal cannula with rate of 40 L/min or higher with FiO2 40%. Criteria for shock included mean arterial blood pressure >65 on pressors for more than 60 minutes (Sevransky et al., 2021).

3.3. Intervention

Participants were given intravenous study agents ascorbic acid (1.5 gram), thiamine (100 mg), and hydrocortisone (50 mg) or a placebo within 4 hours of randomization and then four times a day until the participants were discharged from the intensive care unit or died. The clinical team was not blinded to the use of corticosteroids, and they could give the participants up to 200 mg of hydrocortisone (Sevransky et al., 2021).

3.4. Variables

According to Sevransky et al. (2021), the study's primary outcome was to measure ventilator and vasopressor-free days after administration of study agents in the first month. The second main objective of the study was to estimate mortality in the first month. Moreover, reduction in the intensive care unit length of stay, delirium, mortality, and improvement in kidney functions were other outcomes explored to support the efficacy of the treatment. Hypersensitivity, nephrolithiasis, injection site complication, and hemolysis were included in the Safety endpoints (Sevransky et al., 2021).

3.5. Analysis

In the statistical analysis, categorical data was reported in percentages and frequencies and continuous data (variables) as means with standard deviation and medians with interquartile ranges. In the primary analysis, Sevransky et al. (2021) calculated ventilator and vasopressor free time using medians and interquartile, and 95% confidence interval and *P* value (*P*=0.022) were used to report bivariable differences between intervention and placebo groups, and mortality was reported as a percentage.

3.6. Results

A total of 3243 participants in 43 hospitals were screened, and 501 participants were included in the study (median age 62, 54% male, 46% females, 41% on ventilator and vasopressor, 21% on ventilator alone, and 38% on vasopressor alone). After the screening to determine eligibility, 252 participants were randomly assigned to the intervention group and 249 to the placebo group. Participants had similar characteristics in both groups: disease severity, source of infection, and other comorbid conditions. The median time to start the study intervention (agents) and the onset of shock and respiratory failure was 14.7 hours.

Sevransky et al. (2021) noticed no significant difference in measuring the primary outcome (ventilator and vasopressor-free days) between the intervention group and placebo group, with a confidence interval of 95%, p = 0.85, the median difference in ventilator and vasopressor-free days was -1 day.

The percentage of all-cause mortality was 22% in the intervention group and 24% in the placebo group. Long-term effects were assessed at 180 days, and they noticed that the percentage of mortality was 40.5% in the intervention group and 37.8% in the placebo group (difference, 2.7%; 95% CI, −11.3% to 5.8%). Also, there was no significant difference in the intervention and placebo groups when measuring exploratory outcomes reducing the length of intensive unit stay (*p=0.79),* delirium (*p*=0.45), and improving kidney functions (*p*=0.58).

3.7. Adverse Events

No serious adverse effects were reported in either group. One participant developed hemorrhagic shock, and in one participant, kidney function got worse in the intervention group; Both events were deemed as potential adverse events related to the intervention.

3.8. Biases

One limitation of the study was that it was terminated early due to funding issues, and it was not completed, which could have underpowered the study results. Also, participants' blood concentrations of ascorbic acid were not tested to adjust the dose based on the needs of individuals.

4. Early Administration of Ascorbic Acid, Hydrocortisone, and Thiamin in Septic shock

4.1. Study Design

Lyu et al. (2022) performed a double-masked randomized trial in an intensive unit of a hospital in China. Participants were randomly assigned 1:1 to intervention and placebo groups. Participants who met septic shock criteria were treated with intravenous antibiotics and intravenous fluid for three hours to maintain a mean arterial blood pressure of 65 mmHg. Participants who were not responsive to intravenous fluids were started on norepinephrine within the first hour of diagnosis of septic shock.

Participants in the intervention group received intravenous ascorbic acid (2 gram), hydrocortisone (200mg), and thiamine (200mg) for five days or until they were discharged from the intensive care unit. Clinicians were not blinded to prescribing 200 mg steroids to patients who needed it, for example, patients with chronic pulmonary obstructive disease exacerbation.

4.2. Objectives

The main objective of the study was to measure all-cause mortality at three months. The secondary outcome measured mortality in 28 days, after discharge from the healthcare facility or intensive care unit. Moreover, septic shock resolving rate, time, early discharge from the intensive care unit, reduced length of hospital or intensive care unit stay, and ventilator and vasopressor free time (Lyu et al., 2022).

4.3. Statistical Analysis

Lyu et al. (2022) included 406 participants in the study to project a 90% power for the trial to capture an absolute difference of 15 percent points after a power analysis was performed (Marik et al., 2017).

Luy et al. (2022) noted that data did not have normal distribution using the Shapiro-Wilk and Kolmogorov-Smirnov tests. Thus, the median was reflected for numerical data and percentage for categorical data. Survival time among participants was measured via Cox Proportional Hazard Regression Analysis, and the results were shown as a hazard ratio with a 95% confidence interval.

4.4. Results

According to Luy et al. (2022), 408 participants were included in the study; 203 participants were assigned to the intervention group and 205 to a placebo group. At baseline, the participants had similar characteristics, and they found no significant difference between the intervention group and the placebo group in comorbid conditions, age, sex, site of infection, sequential organ failure score, and acute physiology and chronic health evaluation score (p >0.05).

There was no significant difference in all-cause mortality between groups at three months. The mortality percentage in the intervention group was 40.4% and 39.0% in the placebo group (p=0.77). Also, there was no significant difference between groups for the secondary outcomes including 28 days mortality (p = 0.80), shock reversal time (p = 0.30),
length of stay in the hospital bed (p = 0.35), intensive unit stay (p = 0.85), (Luy et al., 2022).

4.5. Adverse Events and Biases

Common side effects included elevated levels of sodium in the blood, blood glucose dysregulation, and volume overload in both groups. The study was a single-center trial, which impacted its external validity and generalizability. Also, ascorbic acid and thiamin blood levels were not measured, and it was unknown if the amount of given medication met the required blood levels.

5. Effect of Ascorbic Acid, Corticosteroids, and Thiamine on Organ Injury in Septic Shock

Moskowitz et al. (2020) tested the hypothesis that ascorbic acid, corticosteroids, and thiamine can improve Sequential Organ Failure Assessment (SOFA) scores within 72 intensive care unit admissions in patients with septic shock.

5.1. Study Design

A multicenter, randomized, masked, superiority trial was conducted in 14 centers in the United States to compare the combination of ascorbic acid, hydrocortisone, and thiamin with placebo in patients with septic shock (Moskowitz et al., 2020).

5.2. Population

Eligibility for participation included patients aged ≥18 years who were on vasopressor for septic shock and had confirmed or suspected sources of infection. Patients with renal stones, hemochromatosis, glucose-6-phosphate

dehydrogenase deficiency, allergic to investigating drugs, and patients who used the study intervention for other indications were excluded (Moskowitz et al., 2020).

Participants were randomized to intervention and placebo groups with a 1:1 group size. Participants in the intervention groups were intravenous ascorbic acid, hydrocortisone, and thiamine, and the placebo group received a matching amount of normal saline along with standard sepsis management protocols (Moskowitz et al., 2020).

5.3. Outcome

The trial's primary outcome was to improve SOFA score ranges (0 = best and 24 = worst outcome) within 72 hours of enrollment in the study. Secondary outcomes of the study were ventilator and vasopressor free time, reduced all-cause mortality, reduced hospital length of stay, and more rapid intensive unit discharge time.

5.4. Results

A total of 205 participants were randomly assigned with half of them assigned to the intervention group (103) and half to the placebo group (102). Participants in both groups had similar demographic and diagnostic characteristics. Nine participants (9.1%) in the placebo group and 10 participants (9.9%) in the intervention group died before reaching the 72-hour time point. For the primary outcome, Moskowitz et al. (2020) found no statically significant difference between the groups for improvement in the SOFA score (95% CI, -1.7 to 0.2; $p = 0.12$) over 72-hour point time. Furthermore, 64 participants expired within 30 days of enrollment, and for the 30-day mortality, with no statistically significant differences between the intervention and placebo groups (95% CI, 0.8 to -2.2; $p = 0.26$) (Moskowitz et al., 2020). Moskowitz et al. (2020) highlighted that the median number of ventilator-free days within seven days of enrollment for secondary outcomes was not statistically significant between the groups (95% CI, -1.9 to 1.9 days ; $p > 0.99$). They found that the septic shock-free days (number of days in which the patient was alive and needed < 6 hours of any vasopressors) were significantly improved in the intervention group compared to the placebo group (95% CI, 0.2 to1.8 days; $p < 0.01$), and during the first 72 hours, cardiovascular SOFA score in the intervention group (95% CI, -0.9 to-0.1days; $p = 0.3$).

Moskowitz et al. (2020) noticed statically no significant difference between the intervention group and the placebo group for any other SOFA score based on: liver panel (95% CI, −0.3 to 0.1; $p = 0.22$), neurologic elements (95% CI, −0.6 to 0.1; $p = 0.14$), the kidney panel (95% CI, −0.2 to 0.4; $p = 0.52$), the respiratory system (95% CI, −0.3 to 0.3; $p = 0.84$), or the coagulation element (95% CI, −0.2 to 0.2; $p = 0.92$).

5.5. Adverse Events

No serious adverse events were noticed related to drugs under investigation. The most common adverse events were hyperglycemia, hypernatremia, and hospital-acquired infection.

5.6. Limitation of Study

The number of participants in the study by Moskowitz et al. (2020) study is smaller (205), which potentially limits the results' generalizability. Also, the drugs under investigation were administered to the participants 13.5 hours after the administration of vasopressors; the same limitation was noticed in other studies (Annane et al., 2018; Fujii et al., 2020; Venkatesh et al., 2018). Moskowitz et al. (2020) assumed a shorter duration between the initiation of vasopressor and study agent might have resulted in better outcomes.

6. A Prospective, Randomized Clinical Study Comparing Ascorbic Acid, Thiamine, and Hydrocortisone to Hydrocortisone Alone to Determine Decreasing Mortality in Septic Patients

6.1. Objective

Hussein et al. (2021) conducted a prospective randomized clinical trial to assess the difference between triple therapy ascorbic acid, thiamin, and hydrocortisone (ATH) and hydrocortisone (H) alone in decreasing mortality and mitigating organ failure in septic shock patients.

6.2. Study Design

Hussein et al. (2021) conducted a prospective, comparative, randomized study in the Air Force Specialized Hospital in Cairo, Egypt. The study participants were patients who had septic shock on admission or developed septic shock during their stay in the hospital. Criteria for diagnosis of septic shock were the need for a vasopressor to keep mean arterial blood pressure ≥ 65, lactate ≥ 2 mmol/L, and SOFA score ≥ 2 (Bone et al., 1992; Jansen et al., 2010). Participants were randomly assigned 1:1 to the ATH group and H group. Participants in the H group received hydrocortisone, and participants in the intervention (ATH) group received ascorbic acid (1.5 gram), thiamine (200 mg), and hydrocortisone (50 mg) in addition to the standard local protocol for the treatment of septic shock (Hussein et al., 2021).

6.3. Outcome

The study's primary outcome was to assess 28-day mortality in the hospital and intensive care unit. The study's secondary outcome included assessing vasopressor and ventilator-free time, improving liver and renal function, and septic markers such as lactate and procalcitonin (Hussein et al., 2021).

6.4. Results

Participants in both groups had similar socio-demographic, clinical, and biochemical or diagnostic characteristics at baseline. Hussein et al. (2021) found no statically significant differences between the ATH and H group for 28-day intensive care unit and hospital mortality rates ((95% CI = 0.506-1.85, *p* value = .623). Moreover, no significant differences between groups were noticed regarding mechanical free time between the ATH group and the H group. Alternatively, vasopressor-free time was significantly improved in the intervention group ($p = 0.1$).

6.5. Limitation

The study was a single-center study with a small sample size, which limited the generalizability of the study results.

7. A Pilot Study on how Ascorbic Acid, Thiamin, and Hydrocortisone versus Hydrocortisone Alone Effects Microcirculation in Septic Shock Patients

7.1. Objective

Wang et al. (2023) investigated the effects of ascorbic acid, thiamine, and hydrocortisone (ATH), versus hydrocortisone (H) to assess sublingual microcirculation in patients with septic shock.

7.2. Study Design

For this pilot study, a prospective, double-masked, randomized trial method was used to assess the effects of hydrocortisone (H) alone versus ascorbic acid plus thiamin, and hydrocortisone, (ATH) on the perfused small blood vessel density in the sublingual area via side stream dark-field imaging in septic shock patients. Participants were randomly assigned in a 1:1 ratio to the ATH group and the H group. Participants in the treatment (ATH) group received ascorbic acid (1.5 gram), hydrocortisone (200 mg), and thiamine (200mg) in addition to the standard treatment of septic shock. Participants in the H group were treated with hydrocortisone alone in addition to standard treatment for the septic shock Wang et al. (2023).

7.3. Outcome

Wang et al. (2023) defined the perfusion to small vessels as blood vessels 0-20μm in diameter. The study's primary outcome was to assess the small vessel perfusion, which was described as 0 to 20μm in diameter 24 hours after treatment. Wang et al. (2023) used imaging to monitor the perfusion of small blood vessels at baseline, 4 hours, and 24 hours after the initiation of hydrocortisone alone versus ascorbic acid, hydrocortisone, and thiamin. The secondary outcome included an assessment of other blood flow parameters, small vessel density, flow index, and perfusion 24 hours after the initiation of treatment.

7.4. Results

Wang et al. (2023) screened 108 participants and included 27 after applying the exclusion criteria. Participants were randomly assigned: 15 to the ATH group and 12 to the H group. The perfused blood vessel was significantly more in the ATH group than in the H group after 4 hours of treatment (95% CI, 2.227-11.857; $p = 0.009$) and 24 hours (5% CI, 2.390-11.759; $p = 0.008$) (Wang et al., 2023).

7.5. Limitation

The study had a small number of participants (27) and was a single-center study design, which could limit its generalizability.

8. Comparing Ascorbic Acid, Thiamin, and Hydrocortisone to Hydrocortisone Alone in Septic Patients

8.1. Objective

Fujii et al. (2020) investigated the effects of ascorbic acid, hydrocortisone, and thiamin (AHT) compared to hydrocortisone (H) alone to assess septic shock resolving time (mean arterial blood pressure > 65 mmHg without any types vasopressors support for four hours).

8.2. Study Design

Fujii et al. (2020) conducted a multicenter, open-label, parallel-group randomized trial to assess the effects of ascorbic acid (1.5 gram every 6 hours), thiamine (200 mg twice), and hydrocortisone (50 mg every 6 hours) in patients with septic shock in 10 intensive care units in three countries: New Zealand, Australia, and Brazil.

8.3. Study Population

Participants aged≥ 18 years old who were admitted with a diagnosis of septic shock were screened for eligibility. Septic shock was diagnosed based on the Third International Consensus Definitions for Sepsis and Septic Shock which included (a) patient with confirmed and suspected source of infection, (b) 2 points on SOFA score, (c) lactate > 2 mmol/L, and (d) need for a vasopressor to maintain mean arterial blood pressure ≥ 65 for at least two hours at the time of enrollment (Singer et al., 2016; Vincent et al., 1996). Participants were randomly assigned 1:1 to the AHT group and H group. Besides the treatment protocol for septic shock, participants in the AHT group received ascorbic acid, hydrocortisone, and thiamine, and the H group was given hydrocortisone alone (Fujii et al., 2020).

8.4. Outcomes

The study's primary outcome was vasopressor-free time and reduced mortality rate at day seven after participants were randomized. Secondary outcomes included mortality rates measured at 28-day, 90-day, during intensive care unit, and hospital stay. Other variables for secondary outcomes were 28-day cumulative vasopressor-free days, ventilator-free days, and renal replacement therapy-free days, improvement of SOFA score at day 3, and reduced intensive care unit and hospital length of stay.

8.5. Results

A total of 211 participants were randomized into the intervention (AHT) group (100) and H group (104) from 10 intensive units in Australia, Brazil, and New Zealand (Fujii et al., 2020). Fujii et al. (2020) indicated no significant difference between the intervention (AHT) group and the H group in vasopressor free time and reducing mortality rate day 7 after randomization (p =0.83).

For secondary outcomes, there was no significant difference between the ATH group and the H group in all-cause mortality at 28 days (p = 0.69) and 90 days (p = 0.51). Also, Fujii et al. (2020) found no significant difference in 28-day cumulative vasopressor time (p = 0.66), mechanical ventilator time (p = 0.73), and renal replacement therapy time (p = 0.73) between the ATH group and the H group.

8.6. Adverse Events

No serious adverse events were noticed with the intervention under investigation. One participant developed gastrointestinal bleeding in the H group, and two participants in the ATH group were reported to have volume overload and hyperglycemia.

8.7. Limitations

According to Fujii et al. (2020), one of the significant limitations of the study was that it was open-label and did not entail masked outcome assessment. The level of thiamine was not measured in the blood of participants in the intervention group. The sample size was small (211).

9. Evaluating the Effects of Hydrocortisone, Ascorbic Acid, and Thiamine in Septic Shock Patients

9.1. Objective

Mohamed et al. (2023) aimed to assess the effects of hydrocortisone, ascorbic acid, and thiamine on the mortality of septic shock patients.

9.2. Study Design

The study compared the effects of ascorbic acid (1.5 gram), hydrocortisone (50 mg), and thiamine (200 mg) combined with standard treatment versus standard treatment with hydrocortisone alone in a multicenter, randomized, open-label, two-arm parallel-group, pragmatic trial.

9.3. Population

Participants of the study were patients older than 18 with a diagnosis of septic shock that required vasopressor to maintain the mean arterial blood pressure >65 and had lactate level of more than 2mmol/L with adequate volume resuscitation **(**Mohamed et al., 2023).

9.4. Outcome

The primary outcome was to assess mortality at 60 days or the time of hospital discharge, whichever came first. The secondary outcomes included SOFA score, time to death, vasopressor free time, and length of stay in the hospital and intensive unit.

9.5. Results

One hundred six participants were randomly assigned 1:1 to the hydrocortisone group (H) and ascorbic acid, hydrocortisone, and thiamine intervention (AHT) group (53). Participants in both groups had similar diagnostic

characteristics at baseline. The primary sources of infections were pulmonary 35.8%, intra-abdominal 27.4%, and urinary 17.9%.

9.6. Primary outcome

There was no statistical difference between the hydrocortisone-only group (H) and the intervention (AHT) group for hospital mortality at the time of discharge or at 60 days (p = 0.41). Moreover, no statistically significant difference was determined in vasopressor free time (p = 0.44), mechanical ventilator duration (p = 0.36), SOFA score at 72 hours (p = 0.16), and intensive unit stay (p = 0.83) (Mohamed et al., 2023).

9.7. Limitation

The study had multiple limitations: it was open-label, small sample size, and was terminated early due to funding issues.

10. Effects of ascorbic acid, thiamine, and glucocorticoids in Sepsis Patients

10.1. Objective

Iglesias et al. (2020) aimed to assess the effects of hydrocortisone, ascorbic acid, and thiamine on the clinical outcomes of septic shock and sepsis patients.

10.2. Study Design

Iglesias et al. (2020) conducted a randomized, double-blinded trial to determine the effects of ascorbic , hydrocortisone, and thiamine in addition to standard septic shock and sepsis treatment. Participants of the study were adults (18 years of age) who were diagnosed with septic shock and sepsis according to the 2016 Surviving Sepsis Campaign criteria (Rhodes et al., 2017).

10.3. Outcomes

The study's primary outcome was improvement in the SOFA score and septic shock resolution.

10.4. Results

Iglesias et al. (2020) randomly assigned 69 participants to the intervention group and 68 to the comparator group. Participants in both groups at baseline had similar socio-demographic and diagnostic characteristics, SOFA scores, laboratory values, and comorbid conditions. The primary sources of infections were pulmonary 43%, urinary system 31%, bacteremia 14%, and abdominal and other 12%. Also, at the time of enrollment, 50% of the total enrolled participants were on mechanical ventilators and 75% on vasopressors.

Iglesias et al. (2020) found a significant difference between the intervention group and the comparator group for the resolution of septic shock (p < 0.001). However, they found no significant change in the SOFA score (p = 0.18). Moreover, Iglesias et al. (2020) indicated that there was no significant difference in the secondary outcomes of intensive unit mortality (p = 0.37) and hospital mortality (p= 0.65).

10.5. Adverse Events

No serious adverse events related to study intervention were reported. One participant with chronic pulmonary obstructive disease hypoxia worsened, and the adverse events committee indicated that it was secondary to the pulmonary condition and was not related to the study intervention.

10.6. Limitation

The number of participants in the study was small and primarily white/Caucasian, which is considered a relative weakness of the study.

11. Discussion

11.1. Ventilator and Vasopressor

Multiple studies investigated the effects of ascorbic acid (vitamin C), thiamine, and hydrocortisone (ATH) with standard sepsis treatment. Sevransky et al. (2021) found no significant effects of ATH on ventilator and vasopressor-free days ($p = 0.85$). Also, Luy et al. (2022) indicated no significant difference in shock reversal time ($p = 0.30$) with the addition of ATH to the standard septic shock treatment. However, Moskowitz et al. (2020) indicated that septic shock-free days (number of days in which the patient was alive and needed < 6 hours of any vasopressors) were significantly improved by adding ATH to the standard septic shock treatment ($p <0.0$). Iglesias et al. (2020) found a resolution of septic shock with the addition of ATH to septic shock standard treatment ($p < 0.001$).

11.2. ATH and SOFA Score

Moskowitz et al. (2020) found no statically significant improvement in the SOFA score (95% CI, -1.7 to 0.2; $p = 0.12$) over 72 hours after adding ATH to septic shock treatment. Mohamed et al. (2023) ($p = 0.16$) and Iglesias et al. (2020) ($p = 0.18$) noted no improvement in the SOFA score at 72 hours after adding ATH to standard septic shock treatment.

11.3. ATH Effects on Inpatient Length of Stay and Mortality

Several studies indicated that the addition of ATH to the standard treatment of sepsis and septic shock did not significantly decrease the intensive care unit and hospital length of stay (Lyu et al., 2022; Moskowitz et al., 2020; Sevransky et al., 2021). Furthermore, there was no significant reduction in the 28-day mortality, 90-day mortality, and 60-day mortality rates ((Fujii et al., 2020; Hussein et al., 2021; Lyu et al., 2022; Mohamed et al., 2023).

12. Recommendations

Based on the conflicting findings in the reviewed trials, it is hard to determine and recommend regular use of ATH in combination with the standard treatment of sepsis and septic shock with the intention that it will improve patient outcomes. More studies in this field might explain if ATH can reduce mortality and morbidity in sepsis and septic shock patients. We recommend that future studies measure the vitamin C level in participants' blood and adjust the dosage of vitamin C to note any improvements or resolution in symptoms and changes in patient outcomes. Furthermore, sepsis and septic shock can be caused by different infectious sources in the human body. It might be more helpful to study if ATH has positive effects on patient outcomes in relation to specific sources of infections. Using this systematic review as a foundation, further application to treatments for sepsis and septic shock needs be investigated.

13. Conclusion

Sepsis and septic shock are common pathways to higher rates of mortality and morbidity. According to the recently reported data, Approximately 20% of deaths are caused by sepsis globally, with a higher financial burden on already stressed healthcare systems. A systematic review of 8 studies was conducted on studies involving the use of vitamin C/ascorbic acid, thiamine, and hydrocortisone in sepsis and septic shock patients. The authors of the clinical trials found no strong evidence for the regular use of vitamin ascorbic acid, thiamine, and hydrocortisone in sepsis and septic patients. So far, study results have conflicting findings, and more studies in the field might provide more information on the effects of ascorbic acid, thiamine, and hydrocortisone in sepsis and septic patients.

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