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Comparison of Hydrocortisone with Combined Hydrocortisone, Ascorbic Acid, and Thiamine as an Adjuvant Therapy on Septic Shock Patients on Mortality: A Systematic Review and Meta-analysis

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Abstract

BACKGROUND: Septic shock is still considered a global health problem because it is the main cause of morbidity and mortality in critical patients. Various clinical studies have proven that intravenous administration of high dose ascorbic acid and corticosteroid helps slow the inflammation cascade. These studies help lower the global sepsis and septic shock burden with cost-effective methods and minimum side effects. We systematically reviewed the comparison between hydrocortisone and hydrocortisone-ascorbic acid-thiamine (HAT) combined therapy as an adjuvant in the mortality rate of septic shock patients.

METHODS: Four databases (PubMed, EMBASE, Scopus, and Cochrane) are comprehensively searched using specific keywords up to October 18, 2021. All published studies on the use of HAT on septic shock patients were collected and reviewed.

RESULTS: Three randomized controlled trials and two controlled trials enrolling 635 patients were included in the study. HAT therapy was found to be not significant in reducing the intensive care unit (ICU) mortality rate (respiratory rate [RR] 0.89 95% confidence interval [CI] [0.60–1.32], p = 0.56), hospital mortality rate (RR 1.2 95% CI [0.90–1.59], p = 0.21), and 28 days mortality (RR 0.95, 95% CI [0.56–1.58], p = 0.83).

CONCLUSION: HAT is ineffective in reducing ICU, hospital, and 28-days mortality in septic shock patients when compared with hydrocortisone therapy, although HAT adjuvant therapy significantly reduces ICU length of stay, ventilator usage duration, and vasopressor usage duration.

Introduction

The Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3) defined *sepsis* as life-threatening organ dysfunction due to irregular host response to an infection [1]. Septic shock is considered part of sepsis with circulation and metabolism abnormality, making the risk of death higher in septic shock than in sepsis. In 2017, there were an estimated 48.9 million sepsis cases globally, making sepsis incidence 677.5 per 100.000 population [2]. Sepsis causes 11 million worldwide deaths, contributing to 20% of all deaths [3]. Although not known clearly, septic shock incidence is calculated to be at around 50–100 cases per 100.000 population in most developed countries [4].

Septic shock is still considered a global health problem due to it being the main cause of morbidity and mortality in critical patients [5]. Septic shock mortality reaches 15–19 million cases per year, with a 52.5% mortality rate in septic shock patients; mostly in poor and developing countries [3], [6]. To this day, there has not been a targeted therapy for sepsis or septic shock. Hence, management heavily relies on early diagnosis and prompt antibiotic administration, IV fluid, and vasopressors [7].

Hydrocortisone, Vitamin C, and thiamine, both individual and combined therapy, have been studied to reduce mortality and cure organ dysfunction. Marik *et al*. identify the correlation between Vitamin C administration and patient mortality [8], [9]. The retrospective analysis study showed a mortality rate reduction of 31.9% and ×3 as a reduction of time needed for vasopressor administration in patients with severe sepsis and septic shock. In addition, Fowler *et al*. also show that Vitamin C administration can lower pro-inflammatory biomarkers and Sequential Organ Failure Assessment (SOFA) scores [10].

Various clinical studies have proven that intravenous administration of high dose ascorbic acid and corticosteroid helps slow the inflammation cascade [10], [11]. These studies help lower the global sepsis and septic shock burden with cost-effective methods and minimum side effects. However, studies that compare hydrocortisone and

hydrocortisone-ascorbic acid-thiamine (HAT) therapy produce different results. This study aims to compare and analyze the effectiveness of hydrocortisone and HAT therapy to understand the clinical results better.

Materials and Methods

Protocol and registration

This study follows the recommendation by the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement [12] (PRISMA, http://links.lww.com/SHK/B299). The protocol for this review is registered in the International Prospective Register of Systematic Reviews (PROSPERO) database (ID: CRD42022296055).

Search strategy

PubMed, EMBASE, Scopus, and Cochrane databases were searched on October – December 2021. Inclusion criteria include septic shock patients older than 18 years old treated in the intensive care unit (ICU), studies in English and randomized controlled trial, cohort, or case-control studies.

Exclusion criteria include non-full text studies, placebo treatment for control, studies with do not resuscitate patients, unequal treatment between study groups, and studies involving >48 h diagnosis of septic shock (Table 1).

Table 1: Search terms and Boolean operators

Database	Search strategy
Pubmed	([septic shock] OR [septicaemic shock] OR [septicemic shock]) AND (hydrocortisone) AND ([vitamin b1] OR [thiamine]) AND ([vitamin c] OR [ascorbic acid]) AND (mortality)
Embase	(“septic shock” OR “septic shock” OR “septicaemic shock” OR “septicemic shock” OR “shock, septic”) AND (“ascorbic acid” OR “vitamin c”) AND (“thiamine” OR “vitamin b1”) AND “hydrocortisone” AND “mortality”
Scopus	([septic AND shock] OR [septicaemic AND shock] OR [septicemic AND shock]) AND (hydrocortisone) AND ([vitamin AND c] OR [ascorbic AND acid]) AND ([vitamin AND b1] OR [thiamine]) AND (mortality)
Cochrane	“septic shock” AND “hydrocortisone” AND (“thiamine” OR “vitamin b1”) AND (“ascorbic acid’ OR “vitamin c”) AND “mortality”

All abstracts were reviewed independently by the author and one independent reviewer. The systematic review and meta-analysis were done from December 2021 to May 2022.

Outcome

Desired outcomes include:

1. ICU and hospital mortality for 30 and 90 days in patients with septic shock
2. Duration of ICU stays in days
3. Ventilation and vasopressor therapy duration (days), starting during ventilator and/or vasopressor usage after sepsis diagnosis
4. Shock diagnosis duration (days), starting during the first septic shock the patient experienced until death or no longer in septic shock.

Data selection

Studies were selected using three steps: Duplicate studies were filtered out, title and abstract screened, and full-text analysis was done by two reviewers according to the PRISMA [12]. Duplicate studies were filtered out using manually and full-text reading were done independently while considering this study’s clinical question with the inclusion and exclusion criteria.

Studies that fulfilled the inclusion and exclusion criteria were reviewed and read independently by two reviewers to ensure suitability and comprehensiveness. Data regarding authors, study design, year of publication, intervention, control intervention, mortality, and level of evidence were taken. Data that were extracted from the study include:

1. Method: Study design, study duration, and study location
2. Patients included in the study: Age, sex, and race
3. Intervention: Treatment duration, dosage regimen, treatment options, and control treatment
4. Result: Patient mortality

Risk of bias

The author uses the Newcastle Ottawa Scale [13] for cohort and case-control studies and the Cochrane Risk of Bias Tool for randomized clinical trials [14]. Two reviewers do the risk of bias analysis independently by two reviewers to ensure objective results.

Data synthesis and confidence in thee cumulative estimate

The author collects study data using Zotero 5.0 software and Review Manager 5.4 (Cochrane Collaboration) software. The fixed-effect model approach is used in the study. A meta-analysis may be conducted if more than 1 study with the required data. The quality of the study is analyzed using the level of evidence by the Oxford Center for Evidence-Based Medicine.

Results

Search results

From a search of four databases (PubMed, EMBASE, Scopus, and Cochrane), 292 studies were

found. After reviewing the studies using the PRISMA statement, the final number was reduced to 5 studies, from which 3 were randomized controlled trials and two controlled trials (Figure 1).

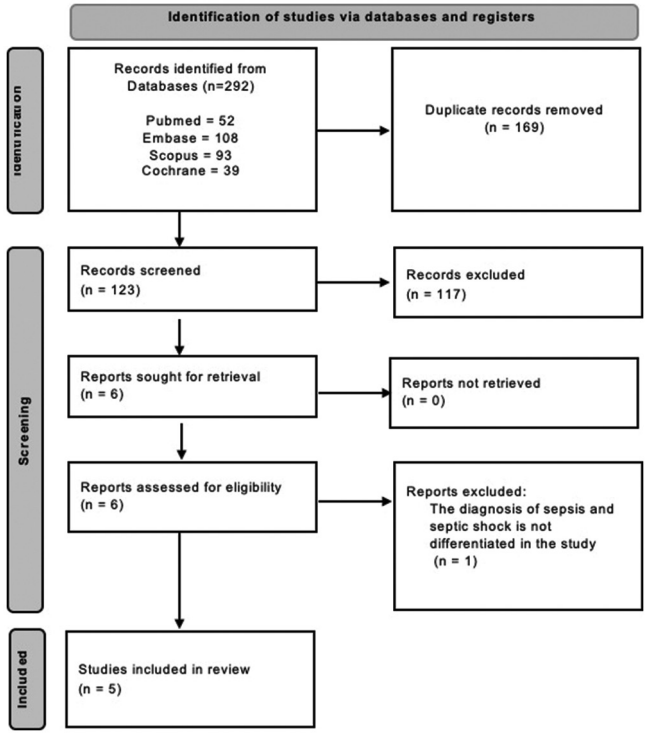

Figure 1: Flowchart of study selection

Risk of bias in the included studies

The risk of bias assessment for the randomized controlled trial studies is done using the Cochrane Risk of Bias Tool for RCT and is presented in supplementary. Newcastle-Ottawa Scale for case–control is used for the controlled trial studies and is presented in Supplementary File. For the three randomized controlled trial studies and two controlled trial studies, the risk of bias is low.

Characteristic of the included studies

Population, intervention, and control

From the studies included, there were 635 subjects included in the studies, 294 were in the HAT group, and 341 were in the hydrocortisone only (Table 2). Populations were subjects diagnosed with septic shock, based on the definitions of Sepsis-3, that was diagnosed within 24 h of hospitalization. All patients were 18 years old or older when they participated in the study, did not have ado-not-resuscitate status, and did not have contraindications for administration of HAT therapy. The majority of the subjects were older than 60 years old, with males making up 58.5% of subjects in the HAT group and 59.2% in the hydrocortisone only group.

The therapy given to subjects in four studies in the control group is hydrocortisone IV 50 mg every 6 h or 200 mg/day. In one study, hydrocortisone is given at 240 mg/day. All subjects were given intervention or hydrocortisone control when vasopressor and tapering-off were done. In the study done by Hussein *et al*. [15], hydrocortisone as an intervention and control is given for 7 days or until discharge from ICU.

In the intervention group or HAT, administration of hydrocortisone is followed by administration of ascorbic acid and thiamine by IV, using the same dose in all the studies. Thiamine is given with a dose of 200 mg/12 h, and ascorbic acid is given with 1.5 g/6 h.

Mortality rate

Mortality rate outcomes can be found in four included studies, where there is a difference in the period cutoff between each study. The mortality rate in the studies was differentiated into ICU mortality, hospital mortality, 28 days mortality, 30 days mortality, and 90 days mortality. Not all studies used the same cutoff period or setting; therefore, not all the data can be compared directly because of the different outcome measures.

Mortality in the ICU setting can be compared between two randomized controlled trial studies and one controlled trial study done by Fujii *et al*., Hussein *et al*. [15], and Long *et al*. [16]. In the study done by Fujii *et al*., the mortality rate for the group receiving HAT therapy was higher (19.6%) compared to the control group, the population of this study is twice the size of the population in the study done by Hussein *et al*. In the study by Hussein *et al*. was found that the ICU mortality in the group receiving HAT therapy was lower (29.7%) when compared to hydrocortisone only therapy. When these two results are compared, the difference is insignificant, with a p-value of 0.80 and 0.2799. In the study done by Long *et al*., a significant difference in the mortality rate is found between the HAT group (11.4%) and the HH group (26%), with a p-value of 0.002.

In the hospital setting, the hospital mortality rate is found in the study done by Coloretti *et al*. [17] and Fujii, *et al*., [11] which showed similar results, in order HAT: HH 60.7%:50% and 23.4%:20.4%. Both of these studies found a higher mortality rate in the group receiving HAT therapy, but both reported that the findings were not statistically significant, with p = 0.254 and p = 0.60.

For the 28 days mortality rate, two studies reported this outcome. In the study done by Fujii *et al*. [11] and Hussein, *et al*. [15], the outcomes are in order HAT: HH 22.6%:20.4% and 36.2%:44.7%. These studies did not report a statistically significant difference (p = 0.69 and 0.4005).

Thirty days mortality and 90 days mortality are only reported in one study, a study by Coloretti *et al*. [17], which shows the mortality rate for 30 days HAT: HH 42.8%:50% and a study by Fujii *et al*.

Table 2: Study characteristics

Author/year	Country	Study design	Study duration	Sample size		Age (year)		Gender	
				HAT therapy	HH control	HAT therapy	HH control	HAT therapy	HH control
Coloretti *et al.*, 2020	Italia	Case control	HAT: June 2017 - November 2019; HH: January 2015 - June 2017	56 patients	56 patients	69 (median)	69 (median)	32 male and 24 female	37 male and 19 female
Long *et al.*, 2020	USA	Case control	January 2018 - June 30, 2019	79 patients	127 patients	64.4 (median)	61.1 (median)	43 male and 36 female	71 male and 56 female
Fujii *et al.*, 2020	Australia, New Zealand, Brazil	RCT	May 2018 - October 2019	107 patients	104 patients	61.9±15.9 (mean±SD)	61.6±13.9 (mean±SD)	68 male and 39 female	65 male and 39 female
Hussein *et al*., 2021	Italy	RCT	August 2019 - November 2020	47 patients	47 patients	65.81±17.02 (mean±SD)	61.60±18.22 (mean±SD)	25 male and 22 female	26 male and 21 female
Reddy *et al*., 2020	India	RCT	-	5 patients	7 patients	53.8±11 (mean±SD)	55.4±12.3 (mean±SD)	4 male and 1 female	3 male and 4 female
Author	Intervention (duration, dose)		Control (duration, dose)		Outcomes				
					Mortality	ICU Length of stay	Ventilator use duration	Vasopressor use duration	Septic shock diagnosis duration
Coloretti *et al.*, 2020	Hydrocortisone IV 240 mg/24 h, ascorbic acid 1.5 g/6 h and thiamine 200 mg/12 h during the use of vasopressors		Hydrocortisone IV 240 mg/24 h, during the use of vasopressors (noradrenaline dose>0.3–0.4 μg/kg/min)		Hospital, n (%): HAT: 34 (60.7); HH: 28 (50) (p=0.254)	HAT: 6 (4–10); HH: 9 (5–15) (days, median-IQR, *P*=0.092)	HAT: 3 (0–8); HH: 6 (2–15) (days, median-IQR, *P*=0.012)	HAT: 3 (2–5); HH: 4 (2–7) (days, median-IQR, *P*=0.533)	-
Reddy *et al*., 2020	(noradrenaline dose > 0.3–0.4 μg/kg/min)		Hydrocortisone IV 200 mg/24 h during the use of vasopressors		-	-	-		HAT: 1860 (749); HH 7422 (8348) min (mean, [SD], *P*=0.17)*
Long *et al.*, 2020	Hydrocortisone IV 50 mg/6 h, ascorbic acid 1.5 g/6 h and thiamine 200 mg/12 h during the use of vasopressors		Hydrocortisone IV 200 mg/24 h during the use of vasopressors		ICU, n (%): HAT: 9 (11.4); HH: 33 (26) (p=0.002) Hospital, n (%): HAT: 21 (26.6); HH: 41 (32.3) (p=0.48)	-	-	-	-
Fujii *et al.*, 2020	Hydrocortisone IV 50 mg/6 h, ascorbic acid 1.5 g/6 h and thiamine 200 mg/12 h during the use of vasopressors		Hydrocortisone IV 200 mg/24 h during the use of vasopressors		ICU, n (%): HAT: 21 (19.6); HH: 19 (18.3) (p=0.80] Hospital, n (%): HAT: 25 (23.4); HH: 21 (20.4) (n=103) (p=0.60) 28 days, n (%): HAT: 24 (22.6) (n=106); HH: 21 (20.4) (n=103) (p=0.69) 90 days, n (%): HAT: 30 (28.6) (n=105]; HH: 25 (24.5) (n=102) (p=0.69)	-	-	-	-
Hussein *et al*., 2021	Hydrocortisone IV 50 mg/6 h for 7 days or until discharge from ICU, followed by tapering off for 3 days. Ascorbic acid 1.5 g/6 h and thiamine 200 mg/12 h for four days or until discharge from ICU		Hydrocortisone IV 50 mg/6 h for 7 days or until discharge from ICU, followed by tapering off for 3 days		ICU, n (%): HAT: 14 (29.7); HH: 19 (40.4) (p=0.2799) 28 days, n (%): HAT: 17 (36.2); HH: 21 (44.7) (p=0.4005)	HAT: 8.319±4.071; HH: 9.787±4.206 (days, mean±SD) (p=0.0889)	HAT: 5.393±3.521; HH: 5.379±3.755 (days, mean±SD) (p=0.9888)	HAT: 4 (3–7); HH: 5 (4–8) (days, median-IQR, *P*=0.0100)	-
Reddy *et al*., 2020	Hydrocortisone IV 200 mg/24 h, ascorbic acid 1.5 g/6 h and thiamine 200 mg/12 h during the use of vasopressors		Hydrocortisone IV 200 mg/24 h during the use of vasopressors		-	-	-	-	HAT: 1860 (749); HH 7422 (8348) min (mean±SD, *P*=0.17)*

HAT: Hydrocortisone-ascorbic acid-thiamine, RCT: Randomized controlled trial, IV: Intravenous, SD: Standard deviation, ICU; Intensive care unit, IQR: Interquartile range, HH: Hydrocortisone only.

for 90 days mortality rate HAT: HH 28.6%:24.5%. None of these results was found to be statistically significant.

The result for mortality outcomes has conflicting results, with some studies reporting higher mortality rates for the HAT intervention group and some reporting otherwise. The only significant result was found in Long *et al*. [16] study, which showed a significantly lower ICU mortality rate in the HAT intervention group with a p-value of 0.002, but no significance in the hospital mortality rate.

ICU length of stay

The outcome for ICU length of stay is reported in two studies written in different formats. Coloretti *et al*. [17] found a significant difference, where the HAT group's length of stay has a median of 6 days compared to the HH group, which has a median of 9 days. Results from the study by Hussein *et al*. [15], Reddy *et al*. [18] reported the length of stay in an average ± standard deviations, where no significant result was found between the two groups (HAT: HH, 8.319 ± 4.07: 9.787 ± 4.206), with a p-value of 0.0889.

Duration of ventilator use

In the study done by Coloretti *et al*. [17], a significant result is found between the HAT group and HH group in ventilator use, with a median duration of 3 days for the HAT nine days for the HH group. Hussein *et al*. [15] reported a non-significant result with a p-value of 0.989. The HAT group's average ventilator use duration is 5.393 ± 3.521, and the HH group is 5.379 ± 3.755.

Duration of vasopressor use

Coloretti *et al*. [17] did not find a significant result, with a median use of vasopressor in the HAT group of 3 days, compared to 4 days in the HH group. The study by Hussein *et al*. [15] found a significant result in the HAT group, with a median of 4 days, compared to 5 in the HH group with a p-value of 0.01. Both studies have a similar result, where the duration of vasopressor use is shorter in the HAT group.

Duration of septic shock diagnosis

Only one study reported this outcome from the included studies; Reddy *et al*. [18] included data for the duration of shock reversal (based on hemodynamic SOFA 4 to 3) since therapy is administered. No significant difference is found between the HAT group and HH group, with a p-value of 0.17.

Meta analysis

The meta-analysis is done on outcomes that are presented in more than one study, in the same study design, and have the same inclusion and exclusion criteria for patients. The outcome that is found to have both is ICU mortality, hospital mortality, and 28 days mortality rate.

ICU mortality

Based on Figure 2, no significant difference is seen in the relative risk of ICU mortality between the control group and intervention group (respiratory rate [RR] 0 89 95% confidence interval [CI] [0.60–1.32], p = 0.56), but we can see a trend that shows HAT therapy may reduce the mortality rate in the ICU. Based on the heterogeneity test, no significant heterogeneity is found with a test result of I2 = 0%, p = 0.35.

Hospital mortality

Based on Figure 3, we found that the relative risk for hospital mortality between HAT therapy and the control shows no significant difference (RR 1.2 95% CI [0.90–1.59], p = 0.21); the data shows a trend that HAT therapy may increase the mortality risk when compared to the control group. When testing for heterogeneity, it was found that I2 = 0% with p = 0.88.

28 Days mortality rate

In Figure 4, we see that HAT therapy shows no significant difference in 28 days mortality rate between the intervention and control group (RR 0.95, 95% CI [0.56–1.58], p = 0.83). Based on the heterogeneity test, no significant heterogeneity is found with a test result of I2 = 0%, p = 0.37.

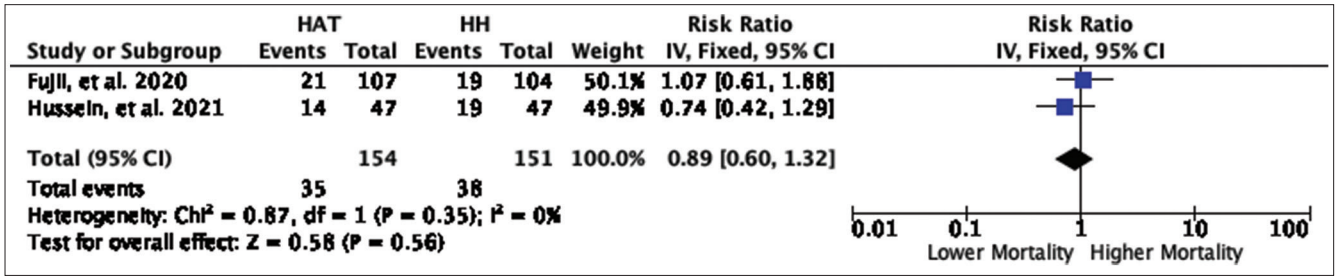

Figure 2: ICU mortality rate

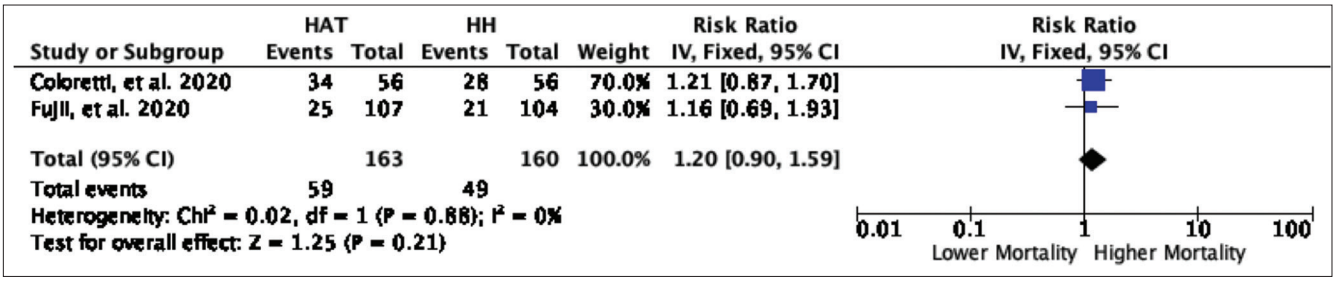

Figure 3: Hospital mortality rate

Discussion

Hydrocortisone, Vitamin C, and thiamine, both individual and combined therapy, have been studied to reduce mortality and cure organ dysfunction. Various clinical studies have proven that intravenous administration of high dose ascorbic acid and corticosteroid helps slow the inflammation cascade [10], [11]. This systematic review discussed the effect of HAT in comparison to hydrocortisone as an adjunct therapy for septic and septic shock patients. Administration of HAT is associated with reducing vasopressor use and SOFA scores during the first 72 h in patients with sepsis and septic shock when compared with standard care. In the Surviving Sepsis Campaign (SSC), the sepsis 2021 management guideline states that hydrocortisone 200 mg daily is only recommended for unstable patients after fluid and vasopressor therapy [19]. Recent guidelines state that corticosteroid IV is recommended for septic shock patients who still need vasopressor therapy.

Sepsis-induced hypotension is characterized by infection-induced systemic vasodilation and increased vascular permeability [20]. These modifications decrease microcirculatory blood flow and tissue perfusion [21]. Systemic inflammation [21], [22] and critical illness-related corticosteroid insufficiency (CIRCI) [23], [24] have been identified as probable causes of sepsis-induced hypotension and hypoperfusion, according to some investigations. Based on these hypotheses, the SSC guidelines for refractory shock and vasopressor dose reduction include prescription corticosteroids, particularly hydrocortisone, for septic shock [7]. However, hydrocortisone alone to treat septic shock is still debatable.

All five studies include a mostly >60 years old male population. This may affect the result of the studies because aging is one of the bad prognostic factors of sepsis incidences with a relatively high mortality rate. Aging causes an increase in coagulation factors and increases the risk of thrombosis and thromboembolism in patients with sepsis. Abnormal cytokine responses are more commonly found in elderly patients than younger patients [9]. These factors affect the higher ICU stay duration.

The study by Coloretti *et al*. [17] shows a hospital and 30 days mortality rate is reduced in the HAT group compared to the hydrocortisone only group with an absolute risk reduction of 7.4% and 10.7%. In the study by Long *et al*. [16], ICU mortality is significantly reduced in the HAT group with an absolute risk reduction of 14.6% and p = 0.002. However, no significance is found in the hospital mortality rate with an absolute risk reduction of 5.7%. The study by Fujii *et al*. shows that both groups have no significant difference whether in 28 days, 90 days, ICU, or hospital mortality. On the other hand, the HAT group has a better SOFA score than the hydrocortisone group. Fujii *et al*. study only measured outcomes from patients who survived 3 days after ICU therapy. Zayed *et al*. [25] study also show a significant SOFA score reduction on the third day of HAT therapy. Mitchell *et al*. study show no significant differences between the two groups. The different dosages of hydrocortisone may cause this. In Mitchell's study, the hydrocortisone given is 10 mg/h.

Chang *et al*. [26] study results contradict Coloretti, *et al*. [17] study results. Chang *et al*. study population have a lower SOFA score (mean: 8.6) than Coloretti's (mean: 11), which may affect the Vitamin C outcome when given to patients with more severe sepsis. Similarly to Chang *et al*., Greenley *et al*. [27] also showed that HAT combination therapy had no

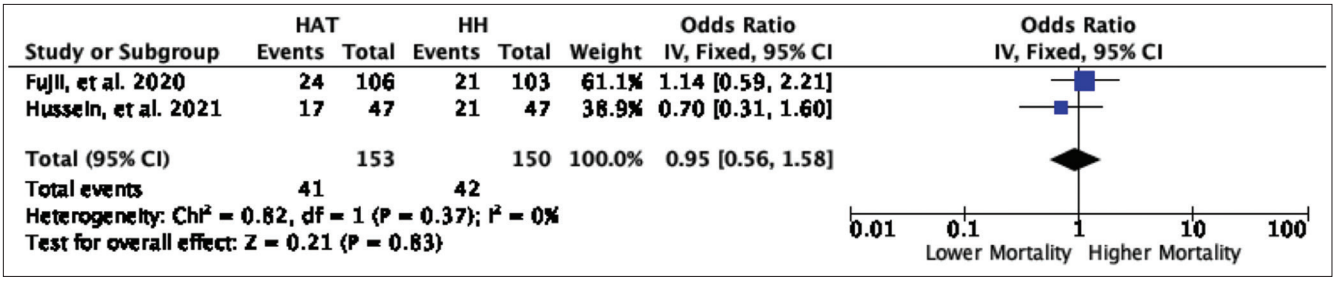

Figure 4: 28 days mortality rate

significant reduction in ICU mortality. In this study, the patients included in the study used more than one vasopressor, which showed the severity of the sepsis. Coloretti and other studies may differ due to Coloretti's limitation in which it uses non-randomized control with a small sample and only taken from one hospital [17], [27].

A reduction in 30 days mortality rate is found in HAT therapy in pediatric patients with septic shock. Wald showed this result, *et al*. [28] the significant reduction may be related to the most common etiology of mortality in pediatric septic shock cases: Refractory shock. HAT therapy may reduce the incidence of refractory shock and mortality rate reduction. Hussein's study showed no significant difference in 28 days and ICU mortality. However, organ recuperation shown by reduction of serum creatinine, AST and ALT are significantly better in the HAT group due to Vitamin C administration. Sepsis patients lack Vitamin C, which increases the risk of cell destruction due to reactive oxygen species. Thiamine plays a crucial role in the Krebs' cycle in which NADPH is produced for ribose 5-phosphate biosynthesis as nucleotide precursor. Around 30% of all septic patients have a thiamine deficiency, especially with the body's hypermetabolic state. Thiamine deficiency also causes cell energy depletion, which leads to mitochondrial failure and cell death. Thiamine administration reduces lactate levels and septic shock mortality.

Coloretti *et al*. [17], Fujii *et al*. [11], and Hussein *et al*. [15] showed that the shorter ICU length of stay in the HAT group is not statistically significant. Hussein's study did not find any significant differences in the duration of mechanical ventilation usage of HAT and hydrocortisone study groups. Reddy's [18] study did not measure the duration of mechanical ventilation usage. Wani *et al*. [29] also found no significant differences in the duration of mechanical ventilation usage of HAT and hydrocortisone study groups. Similarly, Coloretti and Fujii also found no significant differences in the duration of mechanical ventilation usage of HAT and hydrocortisone study groups. HAT administration may affect the duration of mechanical ventilation usage due to Vitamin C, which acts as an antioxidant, steroidogenesis and vasopressin. Reddy's study showed vasopressor usage until reversal shock is longer but insignificant in the hydrocortisone group. Sadaka's study showed that the HAT group needs a longer vasopressor usage duration. However, Sadaka's study has different inclusion criteria, which include septic shock patients with vasopressor therapy. Masood's [30] study showed a significantly shorter vasopressor administration duration in the HAT group.

Coloretti administered hydrocortisone at 240 mg/day. It was given 12 h after shock until patients no longer needed vasopressor. The intervention group in this study was given hydrocortisone with 1.5 g of Vitamin C every 6 h and thiamine as much as 200 mg every 12 h until the vasopressor and steroid were stopped. Vitamin C levels will drop dramatically within 24 h of acute injury, critical illness, multiple organ failure, and sepsis showing how significant HAT initiation time is. All four studies administered HAT therapy for 24 h after sepsis diagnosis. Fujii administered 50 mg of hydrocortisone every 6 h. Some patients in the control group were given thiamine as the doctor's recommendation. Hussein administered the same dose of HAT as Fujii's study. However, Hussein's study administered hydrocortisone for 7 days and HAT for 4 days or until the patient exited ICU. Hussein also includes the tapering off period of 3 days after 7 days of hydrocortisone administration. Reddy's study also includes tapering off 4 days for more than 5 days administered hydrocortisone.

Forty-two patients of each study in Coloretti's study received IgM administration as an adjuvant. In Hussein's study, anti-MRSA and carbapenem are used as antibiotics, given in a series of 1-h septic bundles. In Reddy's study, antibiotics were administered in emergency units, and some patients in the control group received thiamine 100 mg/day if there was any indication.

Other factors that may affect the study's outcome are the amount of Vitamin C and thiamine, which were left unmeasured for each patient before being administered. In addition, each patient's mean arterial pressure target is different depending on the doctor's clinical reasoning. Each patient may have a different medical history. All five studies are non-blinded studies that increase the risk of bias during data extraction.

Several limitations that should be considered that all trials included in this review were lack of blinding. Furthermore, this systematic review did not conduct more subgroup analysis.

Conclusion

The use of hydrocortisone, ascorbic acid, and thiamine (HAT therapy) is not statistically significant in reducing the mortality rate in ICU, hospital, and 28 days survival rate when compared to single hydrocortisone use and more data are needed to conclude. However, the use of HAT adjuvant therapy is found to decrease the duration of care in the ICU, duration of ventilator use, and the duration of vasopressor use compared to single hydrocortisone therapy. The difference in duration of shock diagnosis to the administration of HAT therapy is not found to be significant.

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Supplementary Files

Cochrane risk of bias tool for RCT			
Criteria	Fujii *et al*., 2020	Hussein *et al*. 2021	Reddy *et al*., 2020
Domain 1: Risk of bias arising from the randomization process			
1.1. Was the allocation sequence random?	Y	Y	Y
1.2. Was the allocation sequence concealed until participants were enrolled and assigned to interventions?	Y	NI	NI
1.3. Did baseline differences between intervention groups suggest a problem with the randomization process?	N	N	N
Risk-of-bias judgment	Low	Some concerns	Some concerns
Domain 2: Risk of bias due to deviations from the intended interventions			
2.1. Were participants aware of their assigned intervention during the trial?	NI	NI	NI
2.2. Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?	Y	Y	Y
2.3. If Y/PY/NI to 2.1 or 2.2: Were there deviations from the intended intervention that arose because of the trial context?	N	N	N
2.4. If Y/PY to 2.3: Were these deviations likely to have affected the outcome?	N	N	N
2.5. If Y/PY/NI to 2.4: Were these deviations from intended intervention balanced between groups?			
2.6 Was an appropriate analysis used to estimate the effect of assignment to intervention?	Y	Y	Y
2.7. If N/PN/NI to 2.6: Was there potential for a substantial impact (on the result) of the failure to analyze participants in the group to which they were randomized?			
Risk-of-bias judgment	Low	Low	Low
Domain 3: Missing outcome data			
3.1. Were data for this outcome available for all, or nearly all, participants randomized?	Y	N	N
3.2. If N/PN/NI to 3.1: Is there evidence that the result was not biased by missing outcome data?		N	N
3.3. If N/PN to 3.2: Could missingness in the outcome depend on its true value?		N	PY
3.4. If Y/PY/NI to 3.3: Is it likely that missingness in the outcome depended on its true value?			N
Risk-of-bias judgment	Low	Low	Some concerns
Domain 4: Risk of bias in measurement of the outcome			
4.1. Was the method of measuring the outcome inappropriate?	N	N	N
4.2. Could measurement or ascertainment of the outcome have differed between intervention groups?	N	N	N
4.3. If N/PN/NI to 4.1 and 4.2: Were outcome assessors aware of the intervention received by study participants?	Y	Y	Y
4.4. If Y/PY/NI to 4.3: Could assessment of the outcome have been influenced by knowledge of intervention received?	PN	PN	PN
4.5. If Y/PY/NI to 4.4: Is it likely that assessment of the outcome was influenced by knowledge of intervention received?			
Risk-of-bias judgment	Low	Low	Low
Domain 5: Risk of bias in selection of the reported result			
5.1. Were the data that produced this result analyzed in accordance with a pre-specified analysis plan that was finalized before unblinded outcome data were available for analysis?	N	N	N
5.2. multiple eligible outcome measurements (e.g., scales, definitions, and time points) within the outcome domain?	N	N	N
5.3. multiple eligible analyses of the data?	N	N	N
Risk-of-bias judgment	Low	Low	Low
Overall risk of bias			
Risk-of-bias judgment	Low risk of bias	Low risk of bias	Low risk of bias

NOS for case–control		
Criteria	Long, *et al*.,	Coloretti I, *et al*., 2020
Is the case definition adequate?	★	★
Representativeness of the cases	★	★
Selection of controls		
Definition of controls	★	★
Comparability of cases and controls on the basis of the design or analysis (maximum: ★★)	★	★
Ascertainment of exposure	★	★
Same method of ascertainment for cases and controls	★	★
Non-response rate	★	★
Score/9	8	8

NOS: Newcastle Ottawa Scale, RCT: Randomized controlled trial, ★- yes