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Research Article

Research Article

Combination therapy of thiamine, vitamin C and hydrocortisone in treating patients with sepsis and septic shock: a meta-analysis and trial sequential analysis

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Abstract

Background: The objective of this study was to evaluate the clinical efficacy of thiamine and vitamin C with or without hydrocortisone coadministration on the treatment of sepsis and septic shock.
Methods: MEDLINE, EMBASE and CENTRAL databases were searched for randomized controlled trials (RCTs) that made a comparative study between the combination therapy of vitamin C and thiamine with or without hydrocortisone and the administration of placebo in patients with sepsis or septic shock. Two reviewers independently performed study selection, data extraction and quality assessment. Both short-term mortality and change in the sequential organ failure assessment (SOFA) score from baseline (delta SOFA) were set as the primary outcomes. Secondary endpoints included intensive care unit (ICU) mortality, new onset of acute kidney injury, total adverse events, ICU and hospital length of stay, duration of vasopressor usage and ventilator-free days. Meanwhile, trial sequential analysis was conducted for primary outcomes.

Results: Eight RCTs with 1428 patients were included in the current study. The results showed no significant reduction of short-term mortality in sepsis and septic shock patients who received combination therapy of vitamin C and thiamine with or without hydrocortisone compared to those with placebo {risk ratio (RR), 1.02 [95% confidence interval (CI), 0.87 to 1.20], $p = 0.81$, $I^2 = 0\%$; risk difference (RD), 0 [95% CI, −0.04 to 0.05]}. Nevertheless, the combination therapy was associated with significant reduction in SOFA score [mean difference (MD), −0.63, (95% CI, −0.96 to −0.29, $p < 0.001$, $I^2 = 0\%$] and vasopressors duration (MD, −22.11 [95% CI, −30.46 to −13.77], $p < 0.001$, $I^2 = 6\%$). Additionally, there were no statistical differences in the pooled estimate for other outcomes.

Conclusions: In the current meta-analysis, the combination therapy of vitamin C and thiamine, with or without hydrocortisone had no impact on short-term mortality when compared with placebo, but was associated with significant reduction in SOFA score among patients with sepsis and septic shock.

Key words: Thiamine, Vitamin C, Sepsis, Septic shock, Sequential organ failure assessment, Meta-analysis

Highlights

- High-quality RCTs investigating combination therapy of vitamin C and thiamine for the treatment of sepsis and septic shock were recently published.
- The combination therapy of vitamin C and thiamine, with or without hydrocortisone had no impact on short-term mortality when compared with placebo.
- The combination therapy was associated with significant reduction in SOFA score.

Background

Sepsis is a common yet life-threatening condition due to dysregulated host response toward infection, which is a great burden to healthcare and the social economy globally [1,2]. A recent study suggests an estimate of 11.0 million sepsis-related deaths in 2017 worldwide, accounting for 19.7% of total deaths [3]. For septic shock, a severe subset of sepsis, the mortality is even higher, and can exceed 50% among hospitalized patients [4]. Up to now, the standard management of the septic condition remains infection control by extensive antibiotic therapy in combination with organ support [5]. Given the lack of effective sepsis-specific treatments, novel therapeutic strategies mainly focus on alleviating dysregulated immune responses to improve the clinical prognosis of patients with sepsis and septic shock [6,7].

Deficiencies of vitamin C and thiamine are frequently detected in septic patients, and are reportedly attributed to reduced intake and elevated metabolic requirements [8–10]. Actually, the supplementation of ascorbic acid and thiamine have long been proposed as a promising therapeutic candidate based on various biological mechanisms [10–12]. Both vitamin C and thiamine serve as key components in multiple metabolic processes, and have been proven to alleviate oxidative damage during sepsis, thereby improving endothelial permeability and microcirculatory function [13–15]. Meanwhile, vitamin C was also capable of modulating immune responses, including activation of macrophages and production of inflammatory mediators [10,16]. Furthermore, evidence from observational studies and uncontrolled clinical trials showed a close association between vitamin C and thiamine, either alone or with coadministration of steroids, and improved outcomes in patients with sepsis and septic shock [12,17,18]. However, recently published high-quality randomized controlled trials (RCTs) did not replicate the pro-survival effects of this combination therapy on septic patients, but showed inconsistent results [9,19–25]. A recently published meta-analysis, in which pooled mortality was specifically selected as the primary endpoint, comprehensively assessed the effect of vitamin C alone or in combination with hydrocortisone/thiamine in patients with sepsis and septic shock [26]. Meanwhile, the evidence quality of the previously published meta-analysis was suboptimal due to the inclusion of retrospective observational data [27]. Therefore, we aim to conduct a systematic review and meta-analysis by exclusively incorporating RCTs to evaluate the effects of thiamine and vitamin C with or without hydrocortisone coadministration on mortality as well as amelioration of organ dysfunction among patients with sepsis and septic shock.

Methods

The present meta-analysis was conducted strictly in line with the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) statements [28], and the study protocol was registered with PROSPERO (registration number: CRD42020206950).

Eligibility criteria

RCTs that compared the combination therapy of vitamin C and thiamine with or without hydrocortisone to the administration of placebo among patients with sepsis or septic shock were included, irrespective of dose and duration.

We chose short-term mortality and changes in the sequential organ failure assessment (SOFA) score from baseline

(delta SOFA [SOFA score after 72 h−baseline SOFA score at enrolment]) as primary outcomes. Short-term mortality was defined as all-cause mortality at the longest follow-up, in which 28-day, 30-day, intensive care unit (ICU) and hospital mortality were equal for the analysis module. Secondary outcomes were listed as follows: ICU mortality, newly emerged acute kidney injury (AKI), total adverse events, ICU and hospital length of stay (LOS), duration of vasopressor usage and ventilator-free days.

Search strategy

Online databases including MEDLINE, EMBASE and CENTRAL were comprehensively searched. Relevant works up to 1 March 2021 were potentially eligible for screening irrespective of language and publication type. We conceived search strategies that involved following Medical Subject Heading (MeSH) terms: 'sepsis', 'shock, septic', 'thiamine' and 'ascorbic acid'. Detailed search strategies of each database are presented in Table S1 (see online supplementary material). Meanwhile, ongoing and unpublished trials, as well as conference abstracts were also hand-searched in order to identify additional studies. Besides, we screened references from the reference lists of eligible systematic reviews and trial registries for eligible studies.

Study selection and data extraction

Two reviewers independently screened the titles and abstracts of relevant studies for eligibility. The full text was subsequently retrieved and determined by the same two reviewers if the abstract of a potentially eligible study failed to convey sufficient information. Disagreement between the two reviewers was resolved by discussion. Otherwise, a consulting group that consisted of 5 experts was involved when a consensus could not be reached. Studies with wrong intervention (sole use of thiamine/vitamin C), incorrect participants, wrong study design (prospective or retrospective) and no outcomes of interest were excluded. Duplicate or secondary analyses of included RCTs were also removed.

Two reviewers independently extracted data from all enrolled studies by applying a pre-designed form. We recorded detailed information of eligible studies, including year of publication, first author, sample size, interventions of two arms, participant characteristics as well as clinical settings. In addition, the primary and secondary endpoints were extracted from all included RCTs. Likewise, divergency and inconsistency during the extracting process were resolved through discussion.

Assessment of risk of bias

Two reviewers independently assessed the methodological quality of all enrolled trials in line with the Cochrane risk-of-bias tool, in which each item was scored as high risk, low risk or unclear risk. The following domains were evaluated for each study: randomization sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting, and other bias. In addition, 'other bias' was defined as trials that either had substantial imbalance between intervention and control groups or were sponsored by drug companies and governmental funds. Included RCTs were considered as high quality with low risk of bias when both randomization sequence generation and allocation concealment were evaluated as low risks, while the trials were graded as low quality with high risk of bias under other circumstances.

Data synthesis and statistical analysis

Risk ratios (RRs) and mean differences (MDs) with 95% confidence intervals (CIs) were applied for pooling dichotomous outcomes and continuous data, respectively. Absolute risk difference (RD) was also measured for dichotomous outcomes. Regarding trials reporting LOS as median and interquartile range, LOS was converted into mean and standard deviation, correspondingly, by applying an algorithm proposed by statisticians [29,30].

Methodological and clinical heterogeneity were evaluated based on both the chi-square test and I^2 statistics. Cases with either $I^2 > 50\%$ or p value of chi-square test <0.10 were deemed as having significant heterogeneity. The random effects model and the Mantel–Haenszel method were used for pooling outcomes irrespective of heterogeneity. A two-sided p value <0.05 was considered statistically significant. To assess publication bias across all enrolled RCTs, a funnel plot was constructed and visually inspected for its symmetry. Meanwhile, we also conducted Egger's and Begg's tests to quantitatively evaluate publication bias. Prespecified subgroup analysis and sensitivity analysis were performed to testify the robustness and consistency of our primary endpoints, and to identify potential influencing factors. We stratified all included RCTs by risk of bias, clinical conditions (sole septic shock or sepsis and septic shock) and treatments (combination of vitamin C and thiamine or combination therapy of vitamin C, thiamine and hydrocortisone). Statistical analysis was performed using RevMan version 5.3 (The Nordic Cochrane Centre, The Cochrane Collaboration, Copenhagen, Denmark) and STATA version 12.0 software.

The quality of evidence of each outcome was assessed in accordance with the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) criteria [31], in which each outcome was graded as high, moderate, low or very low. The evaluation was performed by using GRADE Pro software 3.6 (McMaster University 2014, Hamilton, Canada).

Trial sequential analysis (TSA) was performed to reduce the risks of random error due to inadequate sample size and repetitive testing and estimate the required information size (RIS) for this meta-analysis [32]. In addition to RIS, a traditional boundary and an adjusted boundary for

comparing combination therapy of vitamin C and thiamine with or without hydrocortisone to placebo were generated to determine the necessity for performing further RCTs. Type I and Type II errors were set as 5% and 20%, respectively. We performed TSA for both dichotomous and continuous primary outcomes, in which a 20% relative risk reduction and a low-risk-based MD were assigned to calculate optimal information size. TSA was conducted by applying TSA version 0.9.5.10 beta (Copenhagen Trial Unit, Centre for Clinical Intervention Research, Rigshospitalet, Copenhagen, Denmark).

Results

Literature-screening process

The online searches identified 2015 relevant studies. After excluding duplicate records and screening titles and abstracts, 43 studies were potentially eligible for evaluation of full-text. Eventually, 8 RCTs were included in the current systematic review and meta-analysis [9,19–25]. The detailed process of study selection is summarized in Figure 1. Detailed information on important excluded studies and relevant ongoing RCTs are presented in Tables S1 and S2 (see online supplementary material). Additionally, planned and ongoing studies are summarized in Table S3 (see online supplementary material).

The characteristics of included studies

Eight studies with 1428 sepsis or septic shock patients, which compared combination therapy of vitamin C and thiamine with or without hydrocortisone to the placebo, were finally enrolled in the current meta-analysis. Four multi-center trials were conducted [20,21,23,25], while four studies were of single-center design [9,19,22,24]. Four RCTs enrolled patients solely complicated with septic shock [20,21,23,24], whereas four studies included participants with sepsis or septic shock [9,19,22,25]. Seven studies implemented triple therapy, i.e. vitamin C, thiamine and hydrocortisone coadministration [9,19,21–25], whereas one trial applied combination therapy of vitamin C and thiamine [20]. In addition, all included studies were published in full-length articles. Interventions were relatively identical across all included studies, in which a dosing of 1.5 g of vitamin C every 6 h, 200 mg thiamine every 12 h and 50 mg hydrocortisone every 6 h were applied. Meanwhile, patient characteristics were relatively comparable among enrolled RCTs. Detailed information on all included trials is shown in Table 1.

Risk of bias

The risk of bias is summarized in Figures S1 and S2 (see online supplementary material). Three trials were open-labeled [22–24]; one was single-blinded [19]. Performance bias due to lack of blinding might influence all outcomes. Two studies were assessed as having a high risk of selection bias due to inadequate allocation concealment [19,22], including one that also lacked a detailed description of random sequence generation [19]. All these trials were at risk of detection bias due to inadequate blinding of outcome assessment. Attrition bias was unclear in one study due to a lack of detailed description [22]. None of the trials was sponsored by industry, and no reporting bias was detected. Other bias was considered when the study was published only as a meeting report or in abstract form, which was not applicable in our study. Overall, five studies were graded as high-quality [9,20,21,23,25], while three RCTs were deemed as having high risk of bias [19,22,24] (Table 1).

Primary outcomes

Short-term mortality All included studies reported mortality data; four of them presented 28-day or 30-day mortality [19,21,22,25], and in-hospital mortality was provided in the other four studies [9,20,23,24]. Pooling data from seven trials demonstrated no significant reduction in short-term mortality among sepsis and septic shock patients who received combination therapy of vitamin C and thiamine with or without hydrocortisone compared to those with placebo (RR, 1.02 [95% CI, 0.87 to 1.20], $p = 0.81$, $I^2 = 0\%$; RD, 0 [95% CI, −0.04 to 0.05]) (Figure 2). Notably, this outcome was determined to be high-quality based on GRADE criteria (Table 2 and Table S4, see online supplementary material). By performing TSA, the RIS was calculated to be 3492 patients for short-term mortality. Meanwhile, the results of TSA also revealed that the *z*-curve had crossed the adjusted TSA boundary favoring the combination therapy group and control group, indicating no need for further studies to validate the final conclusions (Figure 3).

After excluding three studies with high risk of bias [19,22,24], the estimate of effect remained unchanged (RR, 1.04 [95% CI, 0.85 to 1.28], $p = 0.70$, $I^2 = 0\%$). In another sensitivity analysis, trials enrolling patients with septic shock, and sepsis or septic shock were considered separately. For studies exclusively enrolling septic shock patients [20,21,23,24] and subgroups of sepsis or septic shock patients [9,19,22,25], the combined RR was 1.15 (95% CI, 0.91 to 1.44, $p = 0.24$, $I^2 = 0\%$) and 0.90 (95% CI, 0.72 to 1.14, $p = 0.40$, $I^2 = 0\%$), respectively. Besides, the pooled RR was 1.01 (95% CI, 0.85 to 1.19, $p = 0.94$, $I^2 = 0\%$) and 1.01 (95% CI, 0.85 to 1.20, $p = 0.94$, $I^2 = 0\%$) after removing a trial that applied vitamin C therapy in combination with thiamine without hydrocortisone [20] and a trial that assigned the same dosage of hydrocortisone to both the control group and the intervention group, respectively [23] (Table 2 and Figure S3, see online supplementary material). Furthermore, we performed additional sensitivity analysis by excluding the enrolled studies one at a time from the pooled data, which did not alter the conclusion.

Delta SOFA Delta SOFA was accessible in all included RCTs. When pooled, the combination therapy of vitamin C and thiamine with or without hydrocortisone was associated

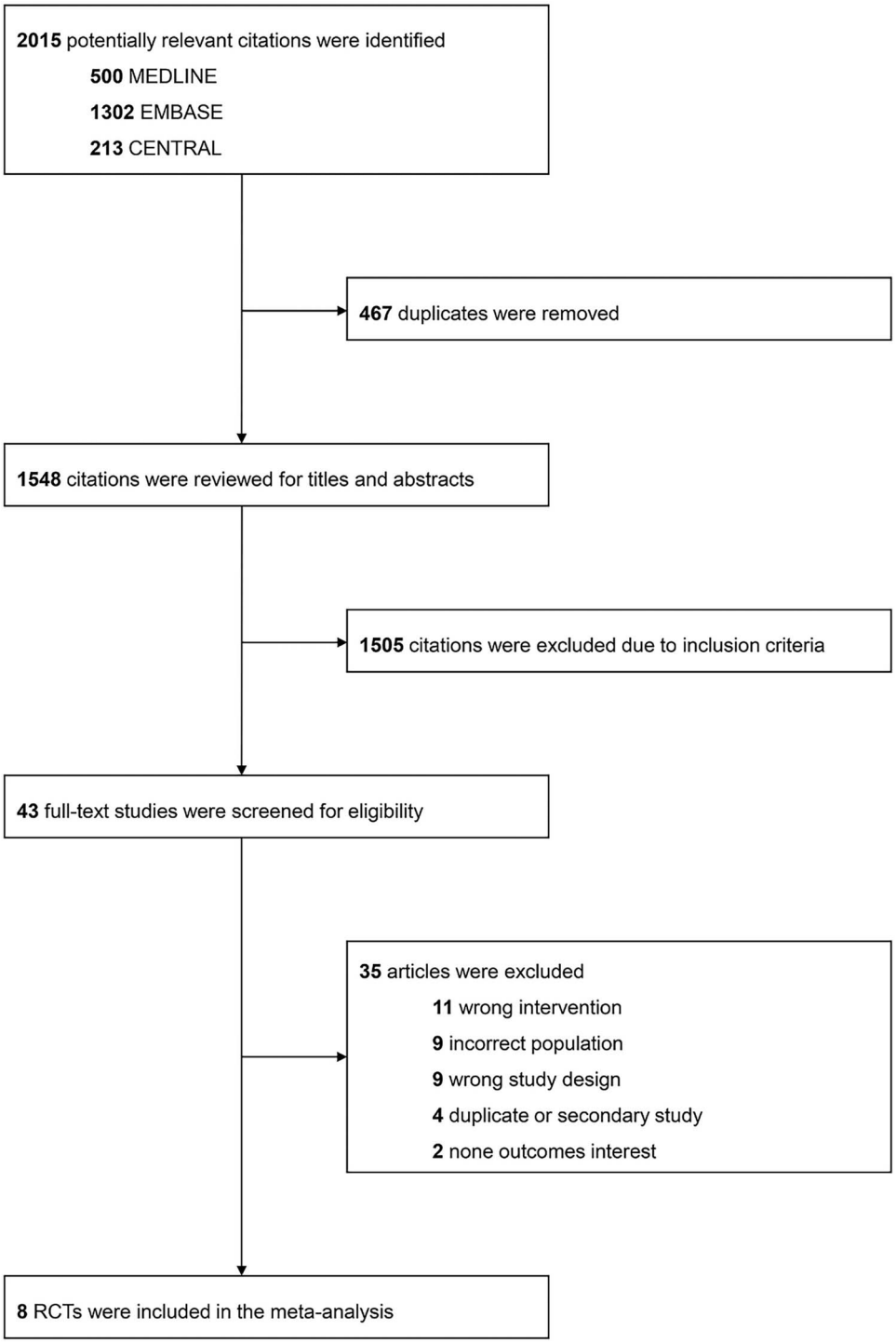

Figure 1. Flow diagram of study selection

with a significant reduction in SOFA score when compared to that in control group MD for delta SOFA, −0.63 (95% CI, −0.96 to −0.29, $p < 0.001$, $I^2 = 0\%$) (Figure 2). Given the results by GRADE framework, delta SOFA was categorized as moderate-quality evidence (Table 2 and Table S4, see online supplementary material). As shown in Figure 3, TSA indicated a total of 2612 patients to be the optimal RIS for the delta SOFA. Of note, the *z*-curve of this endpoint simultaneously crossed both the traditional and adjusted boundaries, hinting that there was no need for further trials to testify this true positive result.

In sensitivity analysis by removing three trials with high risk of bias, the pooled results remained unaltered MD was −0.51 (95% CI, −0.88 to −0.14, $p = 0.007$,

Table 1. Characteristics of included randomized controlled trials comparing combination therapy of vitamin C and thiamine with or without hydrocortisone *vs* placebo among patients with sepsis and septic shock

Study	Sites	Design	Condition	Age	No. participants (male/female)	Intervention		Outcome measurements	Risk of bias
						Combination therapy	Control		
Chang *et al*., 2020 [19]	Single-center	Single-blinded	Sepsis and septic shock	I: 59.5 ± 15.0 C: 63.7 ± 12.8	80 (40/40)	Vitamin C (1.5 g q6h for 4 days or until ICU discharge), thiamine (200 mg q12h for 4 days or until ICU discharge, hydrocortisone (50 mg q6h for 7 days or until ICU discharge).	Placebo (saline)	28-day mortality	High
Fujii *et al*., 2020 [23]	Multicenter	Open-label	Septic shock	61.7 ± 15 I: 69 (IQR, 60–76) C: 69 (IQR: 61–76)	211 (107/104)	Vitamin C (1.5 g q6h for maximum 10 days), thiamine (200 mg q12h for maximum 10 days), hydrocortisone (50 mg q6h for maximum 7 days).	Hydrocortisone (50 mg q6h)	28-day mortality, 90-day mortality, ICU mortality, hospital mortality	Low
Hwang *et al*., 2020 [20]	Multi-center	Double-blinded	Septic shock	I: 70 (IQR, 62–76) C: 69 (IQR, 62–74)	111 (53/58)	Vitamin C (50 mg/kg, maximum single dose 3 g, daily dose 6 g), thiamine (200 mg q12h for 48 h).	Placebo (saline)	7-day mortality, 28-day mortality, 90-day mortality, ICU mortality, hospital mortality	Low
Iglesias *et al*., 2020 [9]	Single-center	Double-blinded	Sepsis and septic shock	I: 70 ± 12 C: 67 ± 14	137 (68/69)	Vitamin C (1.5 g q6h for maximum 4 days), thiamine (200 mg q12h for maximum 4 days), hydrocortisone (50 mg q6h for maximum 4 days).	Placebo (saline)	ICU mortality, hospital mortality	Low
Mohamed *et al*., 2020 [24]	Single-center	Open-label	Septic shock	I: 58.7 ± 14.9 C: 59.4 ± 15.0	88 (45/43)	Vitamin C (1.5 g q6h), thiamine (200 mg q12h), hydrocortisone (50 mg q6h) for 4 days.	Standard care	Hospital mortality	High
Moskowitz *et al*., 2020 [21]	Multicenter	Double-blinded	Septic shock	I: 68.9 ± 15 C: 67.7 ± 13.9	200 (101/99)	Vitamin C (1.5 g q6h for 4 days or until ICU discharge), thiamine (100 mg q6h for 4 days or until ICU discharge, hydrocortisone (50 mg q6h for 4 days or until ICU discharge).	Placebo (saline)	30-day mortality, ICU mortality, hospital mortality	Low
Sevransky *et al*., 2021 [25]	Multi-center	Double-blinded	Sepsis with respiratory/-cardiovascular dysfunction	I: 62 (IQR, 51–69) C: 61 (IQR, 50–72)	501 (252/249)	Vitamin C (1.5 g q6h), thiamine (100 mg q6h), hydrocortisone (50 mg q6h) for 4 days or until ICU discharge.	Placebo	30-day mortality, ICU mortality, 180-day mortality	Low
Wani *et al*., 2020 [22]	Single-center	Open-label	Sepsis and septic shock	I: 59 (IQR, 25–72) C: 56 (IQR, 25–72)	100 (50/50)	Vitamin C (1.5 g q6h for 4 days or until discharge), thiamine (200 mg q12h for 4 days or until discharge), hydrocortisone (50 mg q6h for 7 days or until ICU discharge)	Standard care	30-day mortality, hospital mortality	High

IQR interquartile range, *ICU* intensive care unit, *I* intervention group, *C* control group
q6h and q12h means every 6 hours and every 12 hours, respectively

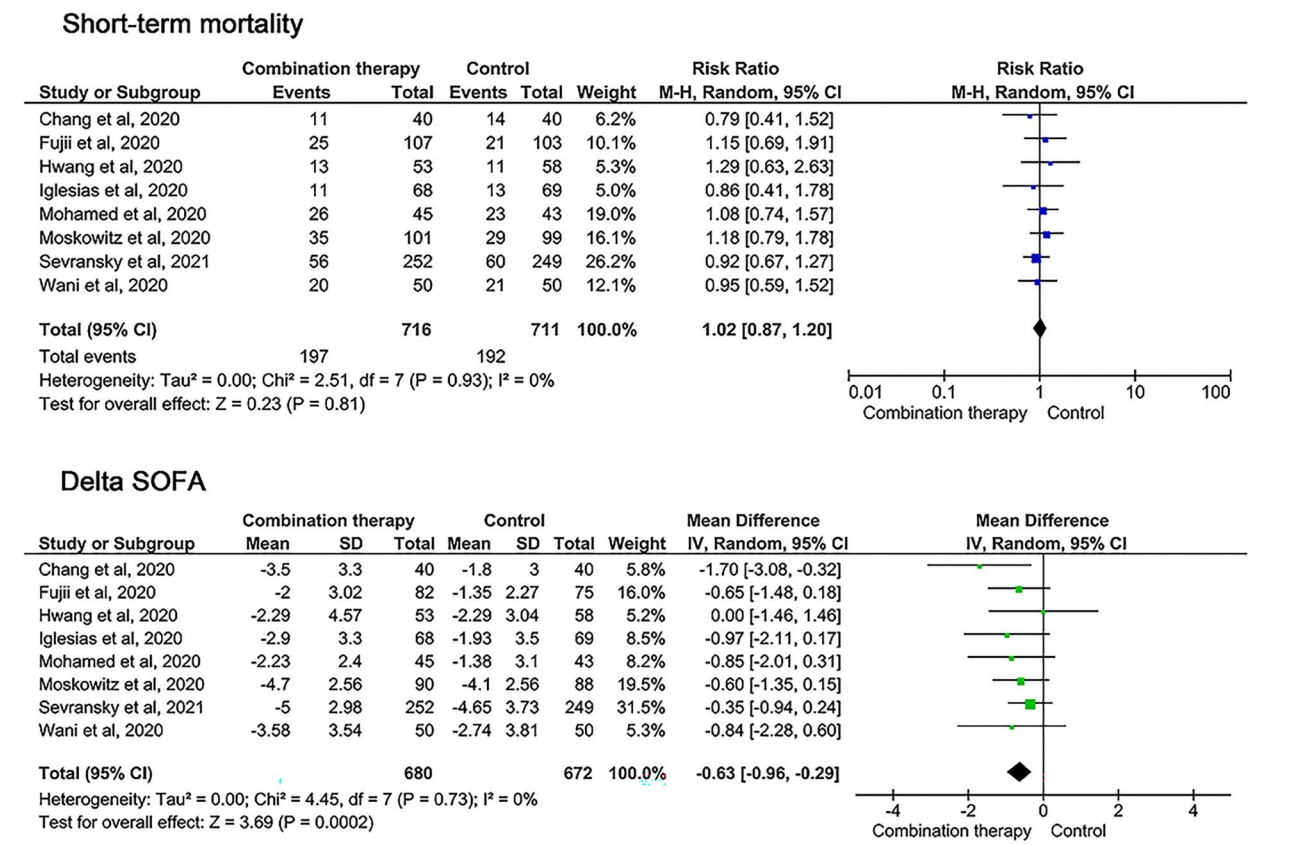

Figure 2. Forest plot for short-term mortality and delta SOFA comparing combination therapy of vitamin C and thiamine with or without hydrocortisone to placebo among septic patients.*CI* confidence interval, *M-H* mantel–Haenszel, *SOFA* sequential organ failure assessment, *IV* inverse variance

I^2 = 0%). Meanwhile, the combined MD was −0.59 (95% CI, −1.07 to −0.12, p = 0.01, I^2 = 0%) and −0.73 (95% CI, −1.28 to −0.18, p = 0.009, I^2 = 16%) for the subgroup of septic shock patients, and sepsis or septic shock patients, respectively. When restricting to the seven studies that implemented triple therapy, the MD estimate was −0.66 (95% CI, −1.00 to −0.32, $p < 0.001$, I^2 = 0%). Similarly, the result confirmed the original finding obtained by excluding the trial that possessed a disparate control group compared to the other studies MD was −0.62 (95% CI, −0.988 to −0.26, $p < 0.001$, I^2 = 0%) [23] (Table 2 and Figure S4, see online supplementary material). Meanwhile, additional sensitivity analysis revealed no change in the current conclusions.

Secondary outcomes

ICU mortality ICU mortality was available in five studies (1147 patients, 214 events) [9,20,21,23,25]. Similarly, the results showed that the administration of vitamin C and thiamine with or without hydrocortisone had no impact on ICU mortality (RR, 1.04 [95% CI, 0.81 to 1.32], p = 0.77, I^2 = 0%; RD, 0 [95% CI, −0.04 to 0.05]; high-quality evidence) when compared to the use of placebo (Table 2 and Figure S5, see online supplementary material).

New onset of acute kidney injury Five studies with 798 patients (335 events) have documented the new events of AKI or kidney failure [9,19–21,23,24]. When pooled, the combination therapy of vitamin C and thiamine with or without hydrocortisone showed no association with the development of AKI (RR, 1.03 [95% CI, 0.91 to 1.15], p = 0.68, I^2 = 0%; RD, 0.01 [95% CI, −0.04 to 0.06]; low-quality evidence) in patients with sepsis and septic shock (Table 2 and Figure S6, see online supplementary material).

Total adverse events By pooling data from five trials (1040 patients, 23 events) [9,19,20,23,25], we demonstrated that the administration of vitamin C and thiamine with or without hydrocortisone resulted in increased risk of adverse events, while the estimate of effect showed no statistical significance with moderate heterogeneity (RR, 2.58 [95% CI, 0.84 to 7.97], p = 0.10, I^2 = 15%; RD, 0.01 [95% CI, −0.02 to 0.04]; very low-quality evidence) in comparison with placebo group (Table 2 and Figure S7, see online supplementary material). A subsequent sensitivity analysis was carried out to validate the robustness of the results by excluding each study one at a time from the pooled estimate. It revealed that the combined RR was driven by the study by Hwang *et al.* [20], which carried 19.7% of the weight. However, the combination therapy of vitamin C and thiamine with or without

Table 2. Summary of outcomes and sensitivity analyses for combination therapy of vitamin C and thiamine with or without hydrocortisone *vs* placebo among patients with sepsis and septic shock

Outcome	No. of events/no. of patients		RD[a] % (95%CI)	Relative risk[b]/Mean difference[c]				Quality of evidence (reason for judgment)
	Treatment	Control		RR (95%CI)	MD (95%CI)	I^2	*P* value	
Primary endpoints								
short-term mortality								High
All studies	197/716	192/711	0 (−4 to 5)	1.02 (0.87 to 1.20)		0%	0.81	
28/30-day mortality[d]	122/433	124/438	−1 (−7 to 5)	0.98 (0.79 to 1.20)		0%	0.82	
Hospital mortality[e]	75/273	68/273	2 (−5 to 9)	1.09 (0.84 to 1.42)		0%	0.51	
Low risk of bias	140/581	134/578	1 (−4 to 6)	1.04 (0.85 to 1.28)		0%	0.70	
High risk of bias	57/135	58/133	−2 (−13 to 10)	0.98 (0.75 to 1.29)		0%	0.90	
Septic shock	99/306	84/303	4 (−3 to 11)	1.15 (0.91 to 1.44)		0%	0.24	
Sepsis and septic shock	98/410	108/408	−4 (−13 to 6)	0.90 (0.72 to 1.14)		0%	0.40	
HVT triple therapy[f]	184/663	181/653	0 (−5 to 4)	1.01 (0.85 to 1.19)		0%	0.94	
Placebo control[g]	172/609	171/608	0 (−5 to 5)	1.01 (0.85 to 1.20)		0%	0.94	
Delta SOFA								Moderate (imprecision)
All studies					−0.63 (−0.96 to −0.29)	0%	<0.001	
Low risk of bias					−0.51 (−0.88 to −0.14)	0%	0.007	
High risk of bias					−1.10 (−1.86 to −0.35)	0%	0.004	
Septic shock					−0.59 (−1.07 to −0.12)	0%	0.01	
Sepsis and septic shock					−0.73 (−1.28 to −0.18)	16%	0.009	
HVT triple therapy					−0.66 (−1.00 to −0.32)	0%	<0.001	
Placebo control					−0.62 (−0.98 to −0.26)	0%	<0.001	
Secondary endpoints								
ICU mortality	109/574	105/573	0 (−4 to 5)	1.04 (0.81 to 1.32)		0%	0.77	High
New onset of AKI	172/398	163/400	1 (−4 to 6)	1.03 (0.91 to 1.15)		0%	0.68	Low (indirectness, imprecision)
Total adverse events	17/520	6/520	2 (−4 to 8)	2.58 (0.84 to 7.97)		15%	0.10	Very low (risk of bias, inconsistency, imprecision)
ICU length of stay					0.04 (−0.58 to 0.67)	0%	0.89	Moderate (imprecision)
Hospital length of stay					0.63 (−0.41 to 1.68)	0%	0.23	Moderate (imprecision)
Duration of vasopressors					−22.11 (−30.46 to −13.77)	6%	<0.001	Moderate (imprecision)
Ventilator-free days[h]					−0.45 (−1.95 to 1.06)	0%	0.56	Moderate (imprecision)

RD risk difference, *RR*, risk ratio, *MD* mean difference, *HVT* hydrocortisone, vitamin C and thiamine, *SOFA* sequential organ failure assessment, *ICU* intensive care unit, *AKI* acute kidney injury

[a]Risk difference < 0.0 favors combination therapy of vitamin C and thiamine with or without hydrocortisone

[b]Risk ratio < 1.0 favors combination therapy of vitamin C and thiamine with or without hydrocortisone

[c]Mean difference < 0.0 favors combination therapy of vitamin C and thiamine with or without hydrocortisone

[d]'28/30-day mortality' refers to the studies inclusively reported mortality data on 28/30 day since randomization

[e]'Hospital mortality' refers to the studies inclusively reported mortality data until hospital discharge

[f]'HVT triple therapy' refers to the studies implemented combination therapy of vitamin C, thiamine and hydrocortisone, rather than vitamin C and thiamine coadministration as intervention

[g]'Placebo control' refers to the studies assigned control group as placebo (normal saline), rather than hydrocortisone administration

[h]The time frame to calculate the ventilator-free days was set to the first 28 or 30 days from enrolment day

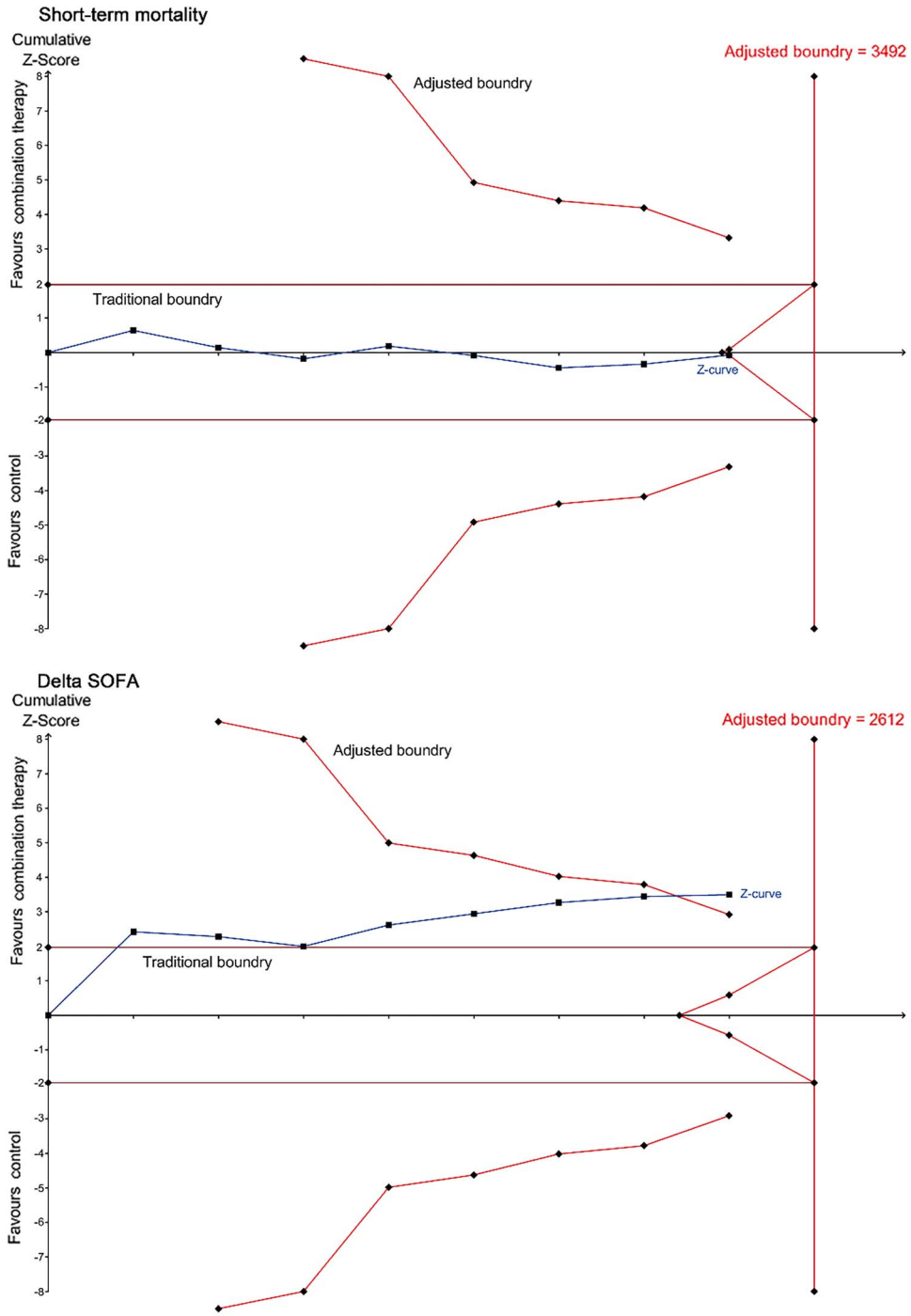

Figure 3. Trial sequential analysis for short-term mortality and delta SOFA comparing combination therapy of vitamin C and thiamine with or without hydrocortisone to placebo among septic patients. The blue *z*-curve was drawn by applying a random effects model. *SOFA* sequential organ failure assessment

hydrocortisone was associated with significantly higher incidence of adverse events without evidence of heterogeneity after excluding Hwang *et al.*'s study (RR, 3.82 [95% CI, 1.41 to 10.35], $p = 0.008$, $I^2 = 0\%$). Since results could be altered by a single study and low observed events with wide confidence intervals, the risk of bias and imprecision were rated as very serious and serious, respectively.

ICU and hospital length of stay The majority of LOS data was reported in the form of medians with interquartile range and was transformed to mean with standard deviation to permit meta-analysis. The LOS in ICU was available in five studies with 898 patients [9,19,20,24,25]. When pooled, we did not observe a significant difference in ICU duration between the intervention and control groups (MD, 0.04 [95% CI,

−0.58 to 0.67], $p = 0.89$, $I^2 = 0\%$; moderate-quality evidence). Similarly, hospital LOS in sepsis and septic shock patients was not significantly correlated with the administration of vitamin C and thiamine with or without hydrocortisone (six studies, 1142 patients; MD, 0.63 [95% CI, −0.41 to1.68], $p = 0.23$, $I^2 = 0\%$; moderate-quality evidence) [9,20,22–25] (Table 2 and Figures S8 and S9, see online supplementary material).

Duration of vasopressors usage and ventilator-free days Three studies with 317 patients reported the duration of vasopressors [9,19,22]. The combined MD was −22.11 (95% CI, −30.46 to −13.77, $p < 0.001$, $I^2 = 6\%$; moderate-quality evidence), indicating that the combination therapy was associated with significantly shortened duration of vasopressors usage when compared to placebo group (Table 2 and Figure S10, see online supplementary material). Sensitivity analysis revealed that the study by Chang *et al.* [19] was the outlier with 10.0% of the weight. After removing this study, the conclusion remained unchanged (MD, −24.02 [95% CI, −32.36 to 15.68], $p < 0.001$, $I^2 = 0\%$), favoring the original conclusions. Additionally, data of 28-day or 30-day cumulative ventilator-free days was accessible in three studies with 847 patients [9,23,25]. Pooling data did not reveal significant difference in ventilator-free days between the intervention and control groups (MD, −0.45 [95% CI, −1.95 to 1.06], $p = 0.56$, $I^2 = 0\%$; moderate-quality evidence) (Table 2 and Figure S11, see online supplementary material).

Publication bias The publication bias for the primary outcomes was evaluated via plotting funnel plots and performing Egger's as well as Begg's tests. Of note, visual inspection of funnel plots did not render concerns that related to publication bias for the primary outcomes (Figures S12 and S13, see online supplementary material). Meanwhile, the results of Egger's (0.913 for short-term mortality; 0.176 for delta SOFA) and Begg's (0.805 for short-term mortality; 0.322 for delta SOFA) tests further revealed that no publication bias existed among all enrolled trials.

Discussion

In the current meta-analysis of RCTs, we found that vitamin C and thiamine, either alone or in combination with hydrocortisone coadministration was associated with a significant reduction in SOFA score and vasopressor duration, but showed no impact on short-term mortality among patients with sepsis and septic shock. Meanwhile, the results also showed no effects of combination therapy on ICU and hospital mortality, new onset of AKI, total adverse events as well as ICU and hospital LOS.

To our knowledge, this is the first comprehensive meta-analysis of RCTs to compare the combination therapy of vitamin C and thiamine with or without hydrocortisone to placebo use in patients with sepsis and septic shock. One research letter assessed the clinical efficacy of hydrocortisone, vitamin C and thiamine (HVT) therapy for septic patients by pooling data from four RCTs and five retrospective studies [27]. The results revealed a pro-survival effect of HVT treatment when pooling data from all enrolled trials (RR 0.46, 95% CI 0.25 to 0.86, $p = 0.01$, $I^2 = 75\%$), while the effect was absent when limited to RCTs (RR 0.92, 95% CI 0.69 to 1.24, $p = 0.59$, $I^2 = 0\%$). The association between HVT treatment and reduction of SOFA score was noted with statistical significance in both RCTs and all enrolled cohorts [27]. Given the limited information in the aforementioned study, our meta-analysis yielded similar results by incorporating data from the recently published and relatively large RCTs [20,21,25]. Additionally, based on results of TSA, the conclusion that combination therapy had no potential effect on improving short-term mortality could be reached without incorporating additional RCTs. Meanwhile, since the *z*-curve of delta SOFA surpassed the traditional boundary and the adjusted TSA boundary, it suggested that there was no need for further RCTs to testify the superiority of combination therapy in alleviating organ dysfunction among patients with sepsis and septic shock. Intriguingly, in a recently published study by Scholz *et al.* investigating the effects of vitamin C therapy (monotherapy or in combination with thiamine/hydrocortisone) in sepsis by incorporating both retrospective and prospective trials, they revealed a substantially reduced mortality in two subgroups: treatment duration of 3–4 days and concerning short-term mortality (<30 days) [26]. Of note, the majority of included RCTs in our study applied the treatment for 4 days except for the study by Hwang *et al.* [20] that used a treatment strategy for 48 h, exclusion of which did not yield a significantly improved survival rate. Likewise, no significant reduction of 28-day or 30-day mortality has been observed in our analysis. The results might be attributed to the exclusive inclusion of RCTs and studies involving combination therapy by our meta-analysis.

Although insufficient organ perfusion and disturbed oxygen delivery have long been established as an intrinsic mechanism for organ dysfunction during the course of sepsis and septic shock [33–36],recent studies have demonstrated that sepsis-induced organ dysfunction could be noted without evident signs of decreased perfusion and substantial ischemic injury, hinting that a novel paradigm might be involved in the development of organ dysfunction, such as bioenergetic dysfunction, dysregulated immune response to infection as well as endothelial and microvascular abnormalities [37–44]. Both vitamins C and B1 play indispensable roles in numerous cellular metabolic and antioxidant processes, and their deficiency results in multiple syndromes that share similar pathophysiology features with sepsis, including peripheral vasodilation, coagulation abnormalities, cardiac and endothelial dysfunction [10,45–47]. Of note, serum levels of thiamine and ascorbic acid decline rapidly among patients with critical illness, confirming their critical involvement in a worsening prognosis [11,45,48,49]. Therefore, the supplementation of vitamin C and thiamine have been proposed as an essential remedy for restoring organ function during sepsis and septic shock [8,50]. The phosphorylated

form of thiamine acts as an important cofactor of pyruvate dehydrogenase, thereby maintaining aerobic respiration. However, insufficient thiamine could result in a shift to an anaerobic pathway and increase lactate levels [51,52]. In a pre-clinical study using a canine model of septic shock, thiamine pyrophosphate was capable of facilitating lactate clearance and promoting oxygen consumption [53]. Meanwhile, this effect was further validated in a RCT of thiamine, in which the administration of thiamine could significantly reduce lactate levels and improved mortality among septic shock patients with thiamine deficiency, while having no pro-survival effect in the overall cohort [11].

Likewise, ascorbic acid serves as a potent antioxidant that can directly scavenge free radicals, playing a critical role in restoring endothelial function and microcirculatory flow [16,54]. Additionally, ascorbic acid is also favorable for the immune response via regulating production of proinflammatory mediators and activating T-cells and macrophages [55–58]. Ascorbic acid is also required for the synthesis of endogenous vasopressors and is indispensable for maintaining vasopressor responsiveness [13]. These findings are in keeping with the results of a clinical study that reported a significant improvement in organ injuries, procalcitonin and inflammation in septic patients who received ascorbic acid [59]. Besides, another RCT that included 28 patients with septic shock revealed a close association of ascorbic acid with lower vasopressor doses and mortality rates [60]. The results from a recently published large RCT (CITRIS-ALI) revealed significantly reduced mortality rates in sepsis patients receiving vitamin C monotherapy, and follow-up analysis found reduced SOFA scores at 96 h [61,62]. Meanwhile, infusion of vitamin C was demonstrated to be safe even at extremely high doses, and the dosage of the intravenous administration of vitamin C was relatively homogenous across all studies (~6 g of vitamin C per day) [63]. Of note, vitamin C and hydrocortisone share numerous beneficial effects on septic cases, and it has been well accepted that ascorbic acid and corticosteroids might act synergistically [10,12]. While oxidizing molecules have been identified inhibiting the binding between glucocorticoid and its receptors, the administration of vitamin C has been shown to reverse this inhibition and restore glucocorticoid function [64]. On the other hand, glucocorticoids are reported to up-regulate the expression of the sodium–vitamin C transporter under inflammatory states, which is essential for mediating cellular transportation of ascorbic acid [65,66]. An experimental study using human lung microvascular endothelial cells has testified to the barrier-protective effects of coadministration of ascorbic acid and hydrocortisone under lipopolysaccharide exposure [66].

Although the present study failed to detect any pro-survival effect of this combination therapy among patients with sepsis or septic shock, it did reveal a potentially beneficial effect on alleviating organ injury. The main theoretical rationale for this combination therapy was the relative deficiencies of both ascorbic acid and thiamine during the course of sepsis. However, there was a lack of standardized methods to precisely measure serum levels of vitamins in septic patients, and the causal relationship between vitamin deficiency and worsening prognosis have not been established yet [67]. Therefore, the beneficial effect on short-term mortality might be limited to the subsets with absolute deficiencies of ascorbic acid and thiamine, which could partially explain these results. Correspondingly, future studies should reexamine the effect of this combination therapy specifically in the subpopulations at increased risk of ascorbic acid or/and thiamine deficiency. As indicated by Scholz *et al*., the timing and duration of the treatment should be noted as well [26]. Although they identified a potentially beneficial effect of treatment strategy for 3–4 days in comparison with an extremely short or prolonged regime, we failed to replicate this finding in our analysis. Nevertheless, it has been well-established that administration of antioxidants could be optimal and valid during the early phase of exaggerated inflammatory responses, while becoming harmful upon late onset of immunosuppression [68,69]. Thus, upcoming studies might take the duration and initiation of the regime into consideration. Furthermore, the combination therapy of vitamin C and thiamine did not lead to increased risk of adverse events and is a relatively low-cost treatment, indicating its great prospects for treating patients with sepsis and septic shock. Notably, four studies recorded more frequent adverse events in septic patients receiving combination therapy compared to the placebo group [19,21,23,25], including hypernatremia, hospital-acquired infections, hyperglycemia, gastrointestinal bleeding, fluid overload, hemorrhagic shock and worsening kidney function, while three of the remaining studies documented no adverse events associated with the intervention [9,20,24]. Considering the relatively large population incorporated in the current study, both adverse events and number of patients who developed adverse events seemed to be extremely low, indicating the safety and efficiency of this regime. Moreover, the clinical efficacy and rationale of this therapeutic approach should be tested in future well-designed RCTs, in which researchers should focus more on the subtle improvements of prognosis, including various adverse events, duration of ICU interventional usage and hospital/ICU LOS.

Several limitations should be taken into account when interpreting our findings. Firstly, the reported outcomes varied across the enrolled studies. The 28- or 30-day mortality, ICU mortality and in-hospital mortality were deemed to be equal in the current meta-analysis, which might introduce potential bias. Correspondingly, we conducted subgroup and sensitivity analyses on short-term mortality stratified by outcomes and came to the same conclusions within every single outcome measurement. Secondly, the interventions in control groups were inconsistent, in which merely one trial applied hydrocortisone as control, while the others used placebo (normal saline) or standard care. Although the beneficial effects of hydrocortisone have been confirmed, it remained elusive whether the effect was due to hydrocortisone solely

or the combination therapy of thiamine and vitamin C. Correspondingly, we carried out sensitivity analysis by excluding the study by Fujii *et al*., in which we revealed a significant reduction in SOFA score with no statistical pro-survival effect among septic patients. Meanwhile, Fujii's study reached the same conclusion by assigning the same dosage of hydrocortisone to both control and intervention groups [23]. Given that, we believe that the improvement of organ dysfunction would not be due to the sole effect of hydrocortisone. Meanwhile, the clinical efficacy of thiamine or vitamin C monotherapy have also been well-established. Therefore, more delicately designed network meta-analyses are needed to independently compare various components of this combination therapy. Thirdly, some endpoints were only reported in a few RCTs, which restricted us from setting additional secondary outcomes, including mechanical ventilation-free days, procalcitonin level and lactate clearance. Finally, the subgroup analyses were limited by the study-level nature of the data, and the timing of treatment and severity of sepsis should be taken into consideration as well. Since results from several upcoming trials are about to be released, an update of the systematic reviews and meta-analyses addressing this topic are urgently needed within the next few years.

Conclusions

In the current meta-analysis, the combination therapy of vitamin C and thiamine, with or without hydrocortisone had no impact on short-term mortality when compared with a placebo group. However, it was associated with significant reduction of SOFA score in patients with sepsis and septic shock. Meanwhile, findings on secondary outcomes varied.

Supplementary data

Supplementary data is available at *Burns & Trauma Journal* online.

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Availability of data and materials

All generated or analyzed data of the present study are included in this article and its supplementary materials.

Authors' contributions

YMY, CR, RQY and YBZ conceived the analysis. RQY, YBZ, YY and ZXL extracted all data. YBZ, JYL, LXW and LYZ did quality assessment. RQY, YBZ and CR co-wrote the paper. RQY, YY, ZXL and HBH undertook the statistical analyses. YMY, GSW, FZ and ZFX were consulted for clinical issues. All authors contributed to and revised the final manuscript.

Conflict of interest

None declared.

Abbreviations

RCTs: Randomized controlled trials; PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analysis; SOFA: Sequential organ failure assessment; ICU: Intensive care unit; AKI: Acute kidney injury; LOS: Length of stay; MeSH: Medical Subject Heading; RRs: Risk ratios; MDs: Mean differences; CIs: Confidence intervals; RD: Risk difference; GRADE: Grading of Recommendations, Assessment, Development and Evaluation; TSA: Trial sequential analysis; RIS: Required information size; HVT: Hydrocortisone, vitamin C and thiamine.

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