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SYSTEMATIC REVIEW

Effect of adjunctive vitamin C, glucocorticoids, and vitamin B1 on longer-term mortality in adults with sepsis or septic shock: a systematic review and a component network meta-analysis

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Abstract

We aimed to compare the effects of vitamin C, glucocorticoids, vitamin B1, combinations of these drugs, and placebo or usual care on longer-term mortality in adults with sepsis or septic shock. MEDLINE, Embase, CENTRAL, ClinicalTrials.gov and WHO-ICTRP were searched. The final search was carried out on September 3rd, 2021. Multiple reviewers independently selected randomized controlled trials (RCTs) comparing very-high-dose vitamin C (≥ 12 g/day), high-dose vitamin C (< 12, ≥ 6 g/day), vitamin C (< 6 g/day), glucocorticoid (< 400 mg/day of hydrocortisone), vitamin B1, combinations of these drugs, and placebo/usual care. We performed random-effects network meta-analysis and, where applicable, a random-effects component network meta-analysis. We used the Confidence in Network Meta-Analysis framework to assess the degree of treatment effect certainty. The primary outcome was longer-term mortality (90-days to 1-year). Secondary outcomes were severity of organ dysfunction over 72 h, time to cessation of vasopressor therapy, and length of stay in intensive care unit (ICU). Forty-three RCTs (10,257 patients) were eligible. There were no significant differences in longer-term mortality between treatments and placebo/usual care or between treatments (10 RCTs, 7,096 patients, moderate to very-low-certainty). We did not find any evidence that vitamin C or B1 affect organ dysfunction or ICU length of stay. Adding glucocorticoid to other treatments shortened duration of vasopressor therapy (incremental mean difference, − 29.8 h [95% CI − 44.1 to − 15.5]) and ICU stay (incremental mean difference, − 1.3 days [95% CI − 2.2 to − 0.3]). Metabolic resuscitation with vitamin C, glucocorticoids, vitamin B1, or combinations of these drugs was not significantly associated with a decrease in longer-term mortality.

Keywords: Vitamin C, Sepsis, Systematic review, Network meta-analysis, Hydrocortisone, Thiamine

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Introduction

Recently there has been considerable interest in "metabolic resuscitation" as adjunctive therapy for sepsis and septic shock. Such metabolic resuscitation has generally involved a combination of vitamin C, glucocorticoids, and vitamin B1 or one of its components [1–5]. Vitamin C is depleted in patients with sepsis [6]. After a phase I study of vitamin C suggested dose-dependent improvement in vascular tone and attenuation of organ dysfunction [7], many randomized clinical trials (RCTs) evaluating this therapy have been undertaken. The role of glucocorticoids in sepsis or septic shock has also been extensively investigated [8–10]. A recent systematic review and meta-analysis of RCTs suggested that low dose glucocorticoids do not reduce mortality but are associated with a shorter duration of artificial organ support [8]. Vitamin B1, an essential cofactor in cellular metabolism, is also depleted in patients with sepsis [11, 12], and administration of vitamin B1 has been reported to reduce lactate levels in patients with sepsis [13].

Because a range of combinations of vitamin C, glucocorticoids, and vitamin B1 has been tested, the evidence-base for these treatments is complicated and cannot be summarized by a simple, conventional, pairwise meta-analysis [14]. Accordingly, we conducted a network meta-analysis (NMA) and component NMA to summarize the available evidence concerning these therapies and determine any incremental effect of each component when added to sepsis treatment [15].

Objectives

We aimed to assess whether vitamin C, glucocorticoids, and vitamin B1 alone or in combination improved patient outcomes by comparing the effect of different therapeutic regimens on mortality and other clinical outcomes in patients with sepsis or septic shock.

Methods

We conducted a systematic review with NMA and component NMA. The protocol was registered in PROSPERO (CRD42018103860) with the rationale for the study and detailed analysis methods published prior to data extraction and analysis [16]. Results are reported according to the PRISMA extension for NMA (Supplement 1) [17].

Study selection

We included all RCTs conducted in patients with sepsis or septic shock aged 18 years or older. Sepsis was defined as reported by the original investigators, and septic shock was defined by the presence of hypotension requiring vasopressor support in patients with sepsis. We compared the following interventions: very high dose vitamin C (≥ 12 g/day, vitC (very high dose)); high dose vitamin C (< 12 g, ≥ 6 g/day, vitC (high dose)); vitamin C (< 6 g/day, vitC); low-dose glucocorticoid (< 400 mg/day of hydrocortisone [or equivalent]); vitamin B1 (any dose, vitB1); and any combinations of the drugs above; regardless of the duration. Where the doses were determined in the unit of mg/kg, we used the following thresholds: ≥ 150 mg/kg/day for vitC (very high dose); < 150 mg/kg/day, ≥ 75 mg/kg/day for vitC (high dose); < 75 mg/kg/day for vitC; and < 5 mg/kg/day of hydrocortisone for glucocorticoid. The cutoff values of vitamin C doses were determined according to the doses used in key trials [1, 2, 7], so that the intervention arms were separated into different treatment groups. We included interventions using corticosteroids containing mineralocorticoids. We excluded those arms that assessed oral or enteral administration of these drugs. The comparators set consisted of all the interventions listed above and a placebo or usual care arm.

Take-home message

Metabolic resuscitation with vitamin C, glucocorticoids, vitamin B1, or combinations of these drugs was not proven to decrease longer-term mortality; and further clinical trials examining the suggested effect of vitamin C (≥ 6 g/day) appear justified.

The primary outcome was longer-term mortality, defined as mortality at the longest follow-up within 90-days to 1-year post enrolment [18]. Secondary outcomes were the severity of organ dysfunction over 72 h measured by the sequential organ failure assessment (SOFA) score or similar, time to cessation of vasopressor therapy, and length of stay in intensive care unit (ICU).

Data sources

We searched Ovid MEDLINE, Embase, and Cochrane Central Register of Controlled Trials without any limitation concerning the year of publication or language (Supplement 2): We also screened previously published meta-analyses for relevant citations. The electronic search was supplemented with searches for published, unpublished and ongoing studies in ClinicalTrials.gov and WHO-ICTRP (Supplement 2). All databases were searched on January 1st, 2021, and the Ovid MEDLINE search was updated on September 3rd, 2021.

Screening, data collection and analysis

Screening and data extraction were conducted in duplicate by eight investigators (TF, AB, YT, AP, NL, CS, FY, and YL) independently. Any disagreement was resolved through discussion or consultation with an additional investigator as pre-defined protocol [16].

Extracted data included the study population (e.g. vasopressor dependency), study interventions, industrial sponsorship, blinding, and outcomes. We contacted the original trial authors if data were missing or unclear.

The risk of bias was assessed using the RoB 1.0 tool by at least two independent reviewers [19]. The overall risk of bias in each study was classified as low, moderate, or high, according to the pre-defined criteria as follows. Low risk of bias: none of the domains were rated as a high risk of bias and allocation concealment was rated as low risk of bias, and three or less were rated as unclear risk. Moderate risk of bias: one was rated as high risk of bias, but allocation concealment was rated as low risk of bias and three or less were rated as unclear risk. High risk of bias: all other cases.

Data synthesis and evaluation of the certainty of the results

We conducted a NMA combining direct and indirect comparisons. We estimated the relative treatment effects using odds ratio (OR) [20] for dichotomous outcomes and mean difference (MD) for continuous outcomes using random-effects models. The reported organ dysfunction scores were all SOFA scores; however, some trials reported the score with modification, i.e. eliminating a component. We, therefore, calculated the standardized mean difference (SMD) to pool these data. The transitivity assumption was evaluated by comparing the distribution of potential effect modifiers across treatment comparisons [21]. We used a side-splitting approach as a local method and the design-by-treatment model as a global method to detect inconsistency in the network [22]. We also estimated the prediction intervals in the results to express the impact of the common heterogeneity assumed across comparisons.

Where possible, we conducted component NMAs to estimate the additive efficacy of therapy components. The component NMA model evaluated the effect of individual components, assuming that the effect of combination therapy was the sum of the effects of its elements. Thus, component NMA identified which elements were essential for the observed effects in the interventions and helps understand how an intervention might work. Results of the component NMA are presented as incremental ORs (iORs), SMDs, or MDs with confidence intervals. An iOR of a component < 1 suggests that the component is associated with decreased mortality when added to sepsis treatment.

We performed the following sensitivity analyses to evaluate the robustness of our findings: (i) mortality at the longest follow-up available in each study (ii) analyzing only studies with a low risk of bias, (iii) analyzing only studies published in 2010 or after for mortality at the longest follow-up, (iv) analyzing time to cessation of vasopressor therapy and ICU length of stay as the ratio of means [23, 24].

We performed all analyses using R version 4.0.1 (R Core Team. 2020 R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria.) NMA was conducted using the netmeta package [25].

The certainty of the network estimates of the primary outcomes was assessed using the framework of Confidence in Network Meta-Analysis (CINeMA) [26]. The CINeMA approach is based on the GRADE framework, which covers six domains of the certainty of evidence: within-study bias, across-studies bias, indirectness, imprecision, heterogeneity, and inconsistency [27]. Changes from the protocol include an extension of screening period of the literature database and an outcome definition in the sensitivity analysis (Supplement 3, eMethods).

Results

We identified 14,914 citations, including 13,416 unique reports. Of these, we assessed 183 full-text articles after excluding 13,233 reports based on the titles and abstracts. We included 43 trials, with 10,257 participants (Supplement 4, eResults 1). The weighted mean age, using studies with age data, was 62.9 years. Three studies were multi-arm trials [7, 28, 29]. One trial compared vitC (very high dose) vs vitC (high dose) vs placebo [7], and we analyzed each arm separately as randomized. Two studies compared two strategies to administer low-dose hydrocortisone vs usual care [28, 29]. The two hydrocortisone arms were combined as one arm of glucocorticoid. Characteristics of the eligible trials and assessments of transitivity are presented in supplementary materials (Supplement 4, eResults 2, 3). Overall, there was no evidence of concern about the transitivity across the comparisons (Supplement 4, eResults 3).

Network meta-analysis

Primary outcome

Of the 43 trials, the primary outcome of longer-term mortality, was reported in 10 trials representing 7,096 participants, comparing vitC (high dose) + glucocorticoid + vitB1, vitC (high dose) + vitB1, glucocorticoid, and control (Fig. 1a) [1, 4, 9, 10, 30–35]. The overall risk of bias was low for four trials (40%) [9, 30, 32, 35], moderate for five trials (50%) [1, 4, 10, 31, 33], and high for one trial (10.0%) [34]. The results from the NMA for longer-term mortality are presented in Figure 2 (orange shaded cells). There was no evidence that vitC (high dose) + glucocorticoid + vitB1, vitC (high dose) + vitB1 or glucocorticoid decreased longer-term mortality compared to

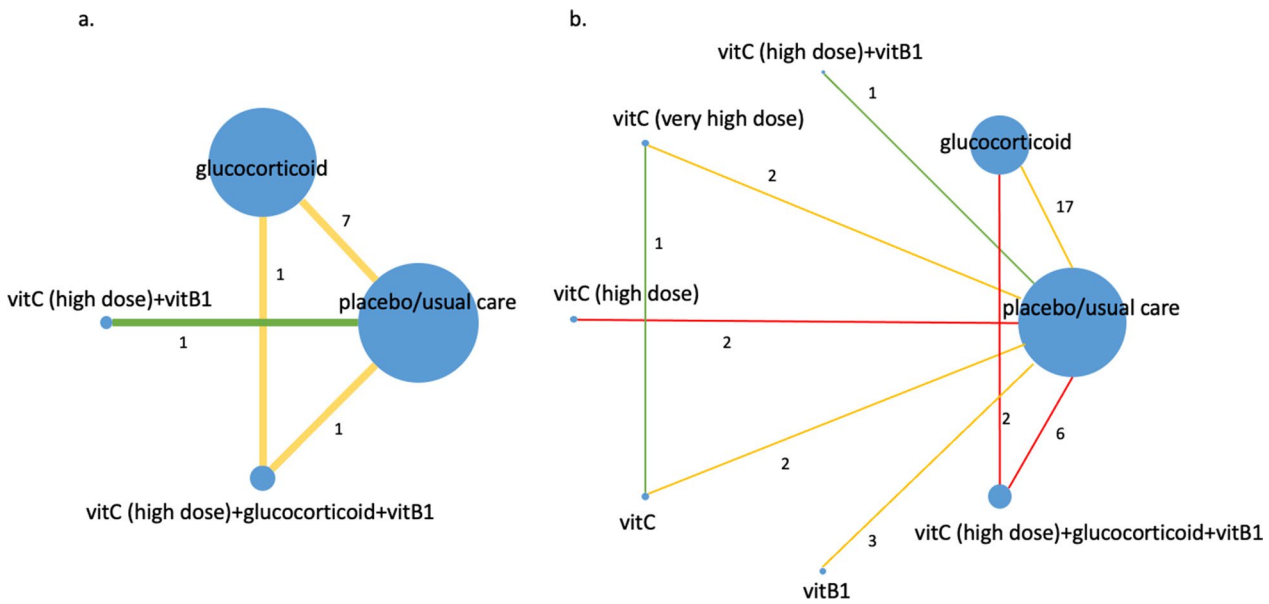

Fig. 1 Network graphs of all available pairwise comparisons between the eligible interventions assessing mortality. The size of the nodes represents the total number of trial arms for each treatment. The number on the edges shows the number of trials for each comparison. The colour of each edge represents the average risk of bias of the contributing studies (green = low, yellow = moderate, red = high). **a** Mortality from 90 days to 1 year. **b** Mortality at the longest follow-up

control. The estimated tau-squared within comparison or network was close to the lower limit of the expected variance (Supplement 4, eResults 4.1). Inconsistency was not detected (Supplement 4, eResults 4.2). Certainty in network estimates was moderate for glucocorticoid vs control; low for vitC (high dose) + glucocorticoid + vitB1 vs glucocorticoid, vitC (high dose) + vitB1 vs control, and vitC (high dose) + vitB1 vs glucocorticoid; and very low for vitC (high dose) + glucocorticoid + vitB1 vs control and vitC (high dose) + glucocorticoid + vitB1 vs vitC (high dose) + vitB1 (Figure 3). Component NMA was not performed because the effects of high-dose vitC and vitB1 were inseparable from the available data.

Secondary outcomes

SOFA scores over 72 h were available from 18 trials with eight arms, representing 2615 patients (Supplement 4, eResults 5.1) [1–3, 31, 33, 35, 37, 38, 43, 47–50, 53, 54, 56–58]. There was no evidence that any intervention was superior to another (Supplement 4, eResults 6). Heterogeneity was suspected in glucocorticoid vs control from visual inspection of the forest plot; however, the estimated variance was close to the expected value (Supplement 4, eResults 5.2). Inconsistency was not detected (Supplement 4, eResults 5.3).

Time to cessation of vasopressor therapy was available from 20 trials with seven arms, comprising 6,206 patients (Supplement 4, eResults 7.1) [4, 7, 28, 31, 33, 34, 36–38, 41–43, 46–48, 50, 57–55, 59]. NMA demonstrated that no intervention shortened the duration of vasopressor therapy (Supplement 4, eResults 8). Heterogeneity was suspected in glucocorticoid vs control from visual inspection of the forest plot (Supplement 4, eResults 7.2). Inconsistency was not detected (Supplement 4, eResults 7.3).

ICU length of stay was available from 24 trials with eight arms, representing 7,308 patients (Supplement 4, eResults 9.1) [1, 3, 4, 7, 10, 13, 28, 31, 32, 34, 35, 38, 40, 41, 46–48, 50, 52–55, 57, 59]. No intervention shortened the length of stay in ICU (Supplement 4, eResults 8). Heterogeneity was suspected in glucocorticoid vs control from the visual inspection of the forest plot (Supplement 4, eResults 9.2). Inconsistency was not detected (Supplement 4, eResults 9.3).

Sensitivity analyses

Mortality at any timepoint was reported in 34 trials, with 9383 patients randomized to eight arms (Fig. 1b). One-year mortality was reported in two trials [30, 31]; 180-day mortality, four trials [1, 9, 32, 36]; 90-day mortality, four trials [4, 33–35]; 30-day mortality, two trials [3, 37]; 28-day mortality, 15 trials [2, 7, 38–50]; 6-day mortality, one trial[51]; in-hospital mortality, four trials [13, 52–54]; ICU mortality, one trial [55]; unknown, one trial [28].

The median of the follow-up periods was 28 days post randomization. The overall risk of bias was adjudicated to

OR 95% CI 95% PrI	All-cause mortality from 90 days to one year post-randomization treatment in the row vs treatment in the column							
All-cause mortality at the longest follow-up post-randomization treatment in the row vs treatment in the column	**placebo or usual care**	0.88 (0.64 to 1.21) (0.58 to 1.33)	0.81 (0.36 to 1.83) (0.29 to 2.26)	No data available	No data available	No data available	1.06 (0.94 to 1.18) (0.88 to 1.26)	No data available
	1.04 (0.82 to 1.33) (0.76 to 1.43)	**vitC (high dose) + glucocorticoid + vitB1**	0.91 (0.38 to 2.20) (0.30 to 2.75)	No data available	No data available	No data available	1.20 (0.86 to 1.66) (0.78 to 1.83)	No data available
	1.24 (0.54 to 2.86) (0.51 to 3.03)	1.19 (0.50 to 2.83) (0.47 to 3.01)	**vitC (high dose) +vitB1**	No data available	No data available	No data available	1.31 (0.57 to 2.99) (0.46 to 3.70)	No data available
	0.53 **(0.29 to 0.99)** (0.27 to 1.05)	**0.51** **(0.26 to 1.00)** (0.25 to 1.05)	0.43 (0.15 to 1.22) (0.14 to 1.30)	**vitC (very high dose)**	No data available	No data available	No data available	No data available
	0.34 **(0.16 to 0.71)** **(0.15 to 0.76)**	**0.33** **(0.15 to 0.71)** **(0.14 to 0.75)**	**0.27** **(0.09 to 0.84)** **(0.08 to 0.90)**	0.64 (0.24 to 1.69) (0.23 to 1.80)	**vitC (high dose)**	No data available	No data available	No data available
	0.85 (0.24 to 3.02) (0.22 to 3.24)	0.81 (0.22 to 2.95) (0.21 to 3.18)	0.69 (0.15 to 3.13) (0.14 to 3.40)	1.6 (0.42 to 6.08) (0.39 to 6.56)	2.5 (0.58 to 10.84) (0.53 to 11.75)	**vitC**	No data available	No data available
	0.98 (0.86 to 1.11) (0.78 to 1.23)	0.94 (0.72 to 1.21) (0.67 to 1.30)	0.79 (0.34 to 1.84) (0.32 to 1.95)	1.84 (0.97 to 3.47) (0.92 to 3.68)	**2.87** **(1.35 to 6.10)** **(1.28 to 6.46)**	1.15 (0.32 to 4.10) (0.30 to 4.41)	**glucocorticoid**	No data available
	1.1 (0.61 to 1.99) (0.58 to 2.10)	1.05 (0.56 to 1.99) (0.53 to 2.11)	0.89 (0.32 to 2.47) (0.30 to 2.64)	2.07 (0.88 to 4.89) (0.82 to 5.19)	**3.24** **(1.26 to 8.35)** **(1.18 to 8.89)**	1.29 (0.32 to 5.23) (0.30 to 5.65)	1.13 (0.62 to 2.06) (0.58 to 2.18)	**vitB1**

Fig. 2 League table for comparisons of mortality from 90 days to 1 year and at the longest follow-up post-randomization

Comparison	Number of studies	Within-study bias	Reporting bias	Indirectness	Imprecision	Heterogeneity	Incoherence	Confidence rating
MIXED EVIDENCE								
glucocorticoid vs vitC (high dose)+glucocorticoid+vitB1	1	Some concerns	Low risk	No concerns	Some concerns	No concerns	No concerns	Low
glucocorticoid vs placebo/usual care	7	Some concerns	Low risk	No concerns	No concerns	No concerns	No concerns	Moderate
vitC (high dose)+glucocorticoid+vitB1 vs placebo/usual care	1	Some concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Very low
vitC (high dose)+vitB1 vs placebo/usual care	1	No concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Low
INDIRECT EVIDENCE								
glucocorticoid vs vitC (high dose)+vitB1	0	No concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Low
vitC (high dose)+glucocorticoid+vitB1 vs vitC (high dose)+vitB1	0	Some concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Very low

Fig. 3 Summary of conidence in network estimates for the primary outcome

be low in 11 trials (34%) [3, 7, 9, 30, 32, 35, 39–41, 44, 49], moderate in eight trials (25%) [1, 2, 4, 10, 31, 33, 36, 38, 43], and high in 15 trials (41%) [13, 28, 34, 37, 42, 49–48, 50–55].

NMA found lower odds ratio for mortality at longest follow-up with high-dose vitC monotherapy than with control, vitC (high dose) + glucocorticoid + vitB1, vitC (high dose) + vitB1, glucocorticoid monotherapy or vitB1 monotherapy (Figure 2, blue shaded cells). The prediction interval of the estimated effect of vitC (very high dose) vs vitC (high dose) + glucocorticoid + vitB1 and vitC (very high dose) vs control showed that the summary effect was very uncertain (Figure 2, blue shaded cells). Detailed assessments of the assumptions and certainty in network estimates are reported in Supplement 4, eResults 10.

When eligible trials were limited to those with low risk of bias, all-cause mortality from 90 days to 1 year was reported only in four trials, and no closed loop in the

Table 1 Estimates of the incremental odds ratios or (standardized) mean differences of each component when added to placebo or usual care

Component	All-cause mortality at the longest follow-up		Severity of organ dysfunction over 72 h	Duration of vasopressor therapy, hours	ICU length of stay, days
		Published in 2010 or after			
	iOR (95% CI)	iOR (95% CI)	iSMD (95% CI)	iMD (95% CI) iROM (95% CI)	iMD (95% CI) iROM (95% CI)
vitC (very high dose)	0.53 (0.28–1.02)	0.5 (0.27–0.92)[a]	0.3 (− 0.3 to 0.9)	− 7.2 (− 75 to 60.6) 0.9 (0.5 to 1.8)	− 1.9 (− 12.4 to 8.6) 0.8 (0.3 to 2.4)
vitC (high dose)	0.62 (0.38–1.02)	0.63 (0.39–1.01)	− 0.4 (− 0.8 to 0.1)	− 11.6 (− 39 to 15.7) 0.7 (0.6 to 0.9)[a]	1 (− 0.9 to 3) 1.1 (0.9 to 1.4)
vitC	0.85 (0.24–3.03)	0.33 (0.06–1.93)	− 0.2 (− 1 to 0.7)	− 43.2 (− 111 to 24.6) 0.5 (0.2 to 1.3)	− 2.9 (− 13.4 to 7.6) 0.7 (0.2 to 2.3)
Glucocorticoid	1 (0.87–1.14)	0.98 (0.88–1.09)	− 0.2 (− 0.4 to 0.1)	− 29.8 (− 44.1 to − 15.5) 0.7 (0.6 to 0.8)[a]	− 1.3 (− 2.2 to − 0.3) 0.9 (0.8 to 1)[a]
vitB1	1.61 (1–2.6)	1.63 (1.03–2.58)[a]	0.3 (− 0.2 to 0.8)	14.2 (− 16.8 to 45.1) 1.3 (1 to 1.6)	0.2 (− 1.9 to 2.2) 1 (0.8 to 1.3)

[a] 95% confidence intervals or 95% prediction intervals do not cross null effect (1 for iOR/iROM, 0 for i(S)MD). In the model of component NMA, adding a component *x* to an intervention A (which includes components other than *x*) leads to an increase of the effects of the intervention *A* that will only depend on *x*, but not on the other components included in *A*. For the case of a binary outcome (e.g., death), this model estimates component-specific iOR, defined as the odds ratio between interventions (*A* + *x*) and *A*. Likewise, for continuous outcomes (e.g., organ dysfunction, duration of vasopressor therapy, and ICU length of stay), the model estimates component-specific iSMDs, iMDs, or iROMs defined as the difference or ratio between interventions (*A* + *x*) and *A*

iOR incremental odds ratio, *CI* confidence interval, *iSMD* incremental standardized mean difference, *iROM* incremental ratio of means, *iMD* incremental mean difference, *vitC* vitamin C (very high dose, ≥ 12 g per day; high-dose, < 12 g per day, ≥ 6 g per day), vitB1 vitamin B1.

network. NMA did not provide any certain result (Supplement 4, eResults 11). Other sensitivity analyses did not result in manifestly different findings from the primary outcome findings (Supplement 4, eResults 6, 12).

Component NMA

Component NMA was performed for the networks where the effects of vitC (very high dose), vitC (high dose), vitC, glucocorticoid, and vitB1 were available separately. None of the components was shown to reduce mortality at the longest follow-up or SOFA score (Table 1). However, the addition of vitC (very high dose) was associated with decreased mortality in studies published in 2010 or after (iOR, 0.5 [95% CI 0.27–0.92]). In contrast, with the addition of vitB1, the iOR for the mortality was 1.63 (95% CI 1.03–2.58) (Table 1). For secondary outcomes, component NMA demonstrated a decrease in the mean duration of vasopressor therapy of − 29.8 h (95% CI − 44.1 to − 15.5) and a decrease in mean ICU length of stay of − 1.3 days (95% CI − 2.2 to − 0.3) when glucocorticoid therapy was added (Table 1).

Discussion

Key findings

In this NMA, metabolic resuscitation with vitamin C, glucocorticoids, vitamin B1, or combinations of these drugs was not shown to reduce longer-term mortality. However, when all available mortality data, including short-term mortality, were evaluated, high dose vitamin C monotherapy was associated with decreased mortality with statistical significance at last follow-up compared with placebo or usual care. However, the treatment effects of vitamins estimated from NMA were of low or very low certainty due to imprecision and possible bias. Component NMA suggested the addition of very high dose vitamin C was associated with decreased mortality. In contrast, vitB1 was associated with increased mortality. Finally, component NMA found that the addition of glucocorticoid therapy decreased the duration of vasopressor support and ICU length without affecting mortality.

Context in reference to prior studies

Many RCTs of vitamin C therapy for sepsis or septic shock have been published, often in combination with glucocorticoid and vitamin B1 [14]. We adopted a NMA design to make the best use of all available data and increase the precision of any effect estimates. We also applied component NMA to separate the effect of each component within bundles of metabolic resuscitation protocols.

We assessed the degree of certainty about reported treatment effects in NMA considering the within-study risk of bias, imprecision, heterogeneity, and incoherence of direct and indirect comparisons. This approach revealed substantial uncertainty about the currently

available evidence for vitamin C monotherapy and its use in combination with glucocorticoids or vitamin B1 for sepsis or septic shock. However, for the first time, component NMA suggested the possible mortality benefit of very high dose vitamin C and possible harm of vitamin B1 by dismantling combination therapies. It also revealed that the addition of glucocorticoid therapy decreased the duration of vasopressor therapy and ICU stay.

Implications for clinical practice and future research

Most vitamin C trials examined the effect of high dose vitamin C in a specific triple-drug regimen, i.e. 6 g/day of vitamin C in combination with glucocorticoid and vitamin B1, and only two arms included very high dose vitamin C or vitamin C. Although data are scarce, our component NMA findings imply that there may be a dose–response relationship between vitamin C therapy and mortality. These observations offer indirect support for further exploration of higher doses of vitamin C therapy in RCTs. Given the sporadic reports of harms related to intravenous high dose vitamin C therapy indicated in a recent scoping review on the adverse effects related to intravenous vitamin C therapy [60], caution should be exercised in using high dose vitamin C outside the context of a clinical trial. Although of great uncertainty, the apparent harm from vitamin B1 suggests that, outside of clinical trials, this therapy should be restricted to septic patients suspected of having beri beri [5].

Our component NMA finding that glucocorticoid therapy was associated with a shorter duration of vasopressor therapy and ICU stay is consistent with large RCTs providing evidence of higher certainty [9, 10]. As glucocorticoid therapy appears to be safe and well-tolerated, these findings provide further evidence for the use of glucocorticoids in patients with septic shock [61].

Limitations

Several limitations should be acknowledged. First, contamination due to co-interventions with other components might have occurred via the network. For example, if a trial allowed glucocorticoid as usual care in comparing vitC versus control, the trial results might have partially reflected the comparison of vitC + glucocorticoid versus glucocorticoid. Such contamination could lead to bias toward the null effect of each intervention. Second, a limited number of RCTs were available for the primary outcome. In particular, RCTs with low risk of bias were scarce. We prespecified longer-term mortality as our primary outcome. We did this because the mortality of patients with sepsis increases steeply in the first 90 days and then gradually plateaus until one year thereafter [18]. Thus, the pre-planned sensitivity analysis using all available mortality data at the last follow-up only provides hypotheses for future trials to examine. Third, missing SOFA scores due to competing risks were not imputed for the analysis. Such missingness tends to occur when patients die or survive to discharge from the ICU before the timepoint of SOFA score assessment [62], and, as such, missingness does not occur at random. Fourth, we performed multiple comparisons. The statistical significance defined by 95%CI is prone to overemphasizing chance findings; however, there are no formal methods to account for such multiplicity in a NMA. Therefore, we limited changes from those pre-specified in the protocol and did not add new analyses without a strong justification. Fifth, heterogeneity was observed in some comparisons. To account for this, we presented the results of the NMA with prediction intervals incorporating the magnitude of heterogeneity. In doing so, we sought to avoid overreliance on the estimated effect measures and the confidence intervals. Sixth, the power and the confidence in the inconsistency tests are low because of the small number of closed loops in all NMAs. Finally, NMA and component NMA should not be considered to provide direct evidence of causal relations between treatments and outcomes because participants in the included trials were not directly randomized in the network.

Conclusions

On NMA, metabolic resuscitation with vitamin C, glucocorticoids, vitamin B1, or combinations of these drugs was not proven to reduce longer-term mortality. However, NMA and component NMA suggested an association of high dose and very high dose vitamin C and decreased mortality with low certainty. Glucocorticoid therapy was associated with a decreased duration of vasopressor support and ICU therapy. Further RCTs evaluating very high dose intravenous vitamin C therapy appear justified.

Supplementary Information
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Author contributions
TF, AB, RB, AC, AAU, and PJY conceived the study. TF, GS, and TAF designed the analysis. TF, AB, NL, YL, AP, CS, YT, and FY screened the records and extracted the data. TF performed the analysis under the supervision of GS. TF, GS, RB, AAU, and PJY interpreted the results and drafted the manuscript. AB, AC, TAF, NL, YL, AP, CS, YT, and FY provided critical revisions to the manuscript. All authors read and approved the final manuscript.

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Availability of data and materials
Dataset is available on request, accompanied by an appropriate scientific rationale and research plan.

Code availability
Code is available in the electronic supplementary materials.

Declarations

Conflicts of interest
None to declare.

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