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Vitamin C therapy for patients with sepsis or septic shock: a protocol for a systematic review and a network meta-analysis

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ABSTRACT

Introduction Vasoplegia is common and associated with a poor prognosis in patients with sepsis and septic shock. Vitamin C therapy in combination with vitamin B_1 and glucocorticoid, as well as monotherapy in various doses, has been investigated as a treatment for the vasoplegic state in sepsis, through targeting the inflammatory cascade. However, the combination effect and the relative contribution of each drug have not been well evaluated. Furthermore, the best combination between the three agents is currently unknown. We are planning a systematic review (SR) with network meta-analysis (NMA) to compare the different treatments and identify the combination with the most favourable effect on survival.

Methods and analysis We will include all randomised controlled trials comparing any intervention using intravenous vitamin C, vitamin B_1 and/or glucocorticoid with another or with placebo in the treatment of sepsis. We are interested in comparing the following active interventions. Very high-dose vitamin C (≥12 g/day), high-dose vitamin C (≥6 g/day), vitamin C (<6 g/day); low-dose glucocorticoid (<400 mg/day of hydrocortisone (or equivalent)), vitamin B_1 and combinations of the drugs above. The primary outcome will be all-cause mortality at the longest follow-up within 1 year but 90 days or longer postrandomisation. All relevant studies will be sought through database searches and trial registries. All reference selection and data extraction will be conducted by two independent reviewers. We will conduct a random-effects NMA to synthesise all evidence for each outcome and obtain a comprehensive ranking of all treatments. We will use the surface under the cumulative ranking curve and the mean ranks to rank the various interventions. To differentiate between the effect of combination therapies and the effect of a component, we will employ a component NMA.

Ethics and dissemination This SR does not require ethical approval. We will publish findings from this systematic review in a peer-reviewed scientific journal and present these at scientific conferences.

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Strengths and limitations of this study

- The effect of intravenous vitamin C, vitamin B_1 or glucocorticoid therapy and that of the combination therapy on clinically important outcomes will be assessed in this systematic review (SR).
- Network meta-analysis (NMA) will address which component(s) of the combination therapy contributes the most to the effect.
- The limitations of primary studies will be addressed with the framework of Confidence in NetworkMeta-Analysis (CINeMA).
- The findings from this SR with NMA has the potential to inform future clinical trials.

BACKGROUND

Vasoplegia, otherwise called vasodilatory shock, is well-recognised in sepsis.[1] It is characterised by the reduced vascular tone and requires escalating exogenous doses of vasopressors to maintain blood pressure even in patients with normal cardiac function. In order to counteract vasoplegia, the human body synthesises and releases norepinephrine, epinephrine, cortisol, vasopressin or angiotensin II through stimulation of baroreceptor and chemoreceptor as well as proinflammatory cytokines. The autonomic system responds immediately to maintain the vascular tone and blood pressure; however, when responsiveness to catecholamines is altered and autonomic control is impaired, the prognosis is poor.[2–4]

To date, glucocorticoids have undergone extensive investigation as an adjuvant treatment to restore vascular responsiveness to vasopressors,[5] and recent large randomised controlled trials have reported a reduced duration of shock and vasopressor use.[6 7]

Vitamin C is an essential water-soluble vitamin that plays an extensive role as an

antioxidant, electron donor and cofactor for many enzymes and proteins in the human body. It suppresses activation of nuclear factor kappa-B[8 9]; a potent proinflammatory mediator which contributes to endothelial dysfunction, activation of coagulation and the cellular injury characteristic of sepsis through increased transcription of multiple proinflammatory cytokines.

Vitamin B_1 (thiamine) works as an essential cofactor in cellular metabolism. In an animal model of septic shock, vitamin B_1 improved haemodynamic instability irrespective of the status of vitamin B_1 deficiency.[10]

Despite having an appealing model of pathogenesis, the effectiveness of vitamin C or vitamin B_1 administration in sepsis is yet to be determined. Recently, the combination of high-dose vitamin C (6 g/day), vitamin B_1 and hydrocortisone was reported to be a possible treatment strategy for septic shock.[11] This before–after study showed a decrease in mortality of patients with septic shock after the implementation of the combination therapy. A number of clinical trials have been conducted since this study was published to assess the effect of combination therapy.[12 13] This combination of interventions appears theoretically reasonable as the three drugs share the same cell signalling pathway or metabolic cascade.[14] To date, at least seven systematic reviews (SRs) have tried to assess the effect of vitamin C on sepsis or critical illness with conservative pair-wise meta-analysis[15–21]; however, the question has become more multidimensional since the evolution of the triple combination therapy, which cannot be addressed with a simple pair-wise analysis. In this regard, network meta-analysis (NMA) is proposed as a useful tool to synthesise the best available evidence where multiple interventions are compared.

Objectives

To assess whether vitamin C, vitamin B_1 or glucocorticoid is effective in patients with sepsis or septic shock and to assess whether their use in combination has a greater efficacy than any of the drugs given alone, by comparing the effect of different therapeutic regimens on mortality, severity of organ dysfunction, duration of vasopressor therapy and the intensive care unit (ICU) length of stay in patients with sepsis or septic shock.

METHODS

Study design

We will perform a SR and NMA, using the guidelines from the Cochrane Collaboration and Centre for Reviews and Dissemination. The protocol is hereby reported according to the Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols guideline[22] (online supplementary file), and the result of the SR will be reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses extension for NMA.[23]

Criteria for considering studies for this review

Types of studies

We will include all randomised controlled trials (RCTs) reported as comparing any intervention using vitamin C, vitamin B_1 and/or glucocorticoid with another or with placebo in the treatment of sepsis or septic shock. We will include vitamin C, vitamin B_1 or glucocorticoid studies only if the study drug was given intravenously. We will include cluster-randomised trials. Cross-over trials will be excluded because of the rapidly evolving nature of sepsis or septic shock. Quasi-randomised trials (such as alternating patients) will be excluded, as such methodology is well-established as a source of bias.[24]

Types of participants

Patients with sepsis or septic shock aged 18 years or older will be included. Studies that included a minority (<10%) of patients under 18 years, or studies with a median or mean age of patients over 20 years will be included. Sepsis will be defined as reported by the original investigators. Septic shock will be defined by the presence of hypotension requiring vasopressor support in patients with sepsis.

Types of interventions

We are interested in comparing the following active interventions: very high-dose vitamin C (≥12 g/day, VHD-vitC); high-dose vitamin C (≥6 g/day, HD-vitC); vitamin C (<6 g/day, vitC); low-dose glucocorticoid (<400 mg/day of hydrocortisone (or equivalent), GC); vitamin B_1 (any dose, vitB_1); and any combinations of the drugs above; regardless of the duration. Where the doses were determined in the unit of mg/kg, then we will use following thresholds: ≥150 mg/kg/day for VHD-vitC; ≥75 mg/kg/day for HD-vitC; <75 mg/kg/day for vitC; and <5 mg/kg/day of hydrocortisone for GC. We will include interventions using corticosteroids containing mineralocorticoids. Such interventions will be classified according to the amount of glucocorticoid contained. We will exclude those arms that assessed oral or enteral administration of these drugs. We will include either arm of head-to-head or placebo (PBO) controlled trials; thus, the synthesis comparator set consists of all the interventions listed above and placebo-controlled trials. Figure 1 shows the network of all possible pairwise comparisons between the eligible interventions. We assume any patient who meets the inclusion criteria is, in principle, equally likely to be randomised to any of the interventions in the synthesis comparator set, which means we can imagine a mega-trial with all treatments in the network being compared.

Types of outcome measures

We will estimate the relative ranking of the competing interventions according to the primary outcome. The primary outcome will be all-cause mortality at the longest follow-up within 1 year but 90 days or longer after randomisation. Secondary outcomes are the severity of organ dysfunction over 72 hours measured by the sequential

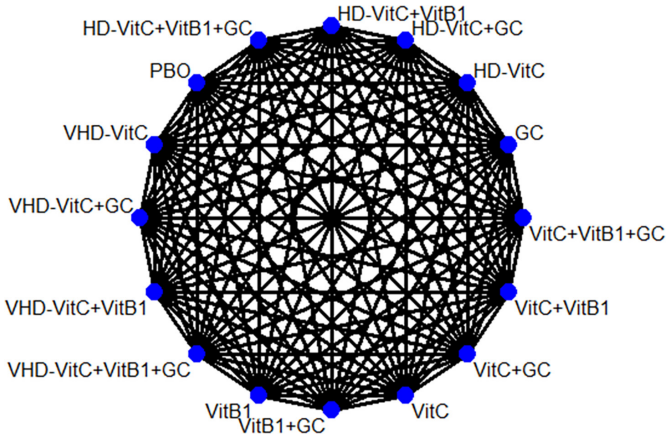

Figure 1 The network structure for all possible pair-wise comparisons.

organ failure assessment score or similar scores, time to cessation of vasopressor therapy and ICU length of stay.

Search methods for identification of studies

Searches for published RCTs will be undertaken in the following electronic databases: Ovid MEDLINE and Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Daily and Versions, Embase Classic+Embase and Cochrane Central Register of Controlled Trials. We will also screen previously published meta-analyses for relevant citations. Supplement presents the search term used in the databases. The electronic search will be supplemented with searches for published, unpublished and ongoing studies in ClinicalTrials.gov and WHO-ICTRP (online supplementary file). We will ask the identified authors as well as experts in the field for any additional, unpublished trials.

Data collection and analysis

Selection of studies and data extraction

Two authors will independently review references and abstracts retrieved by the search and code them as 'retrieve' or 'do not retrieve'. We will obtain the full texts of the retrieved references and use the same criteria to determine which to include or to exclude. We will resolve any disagreement through discussion or, if required, we will consult a third member of the review team. Two reviewers will extract data from the included studies independently using a standardised data extraction form for study characteristics, outcome data and quality rating.

Outcome data

For the primary outcome, we will extract the number of patients who were randomised and of these, the number who were deceased at the longest follow-up within 1 year, but 90 days or longer after randomisation.

For the secondary outcome data, we will extract means, SDs and the number of patients randomised in each study arm. When means and their SDs are unavailable, we will contact study authors to provide the data. When SEs, t-statistics or p values are reported, these will be transformed to SDs. If neither of the above-mentioned measures are reported in the original report or a previous SR, the mean value of known SDs will be calculated from the group of included studies.[25] The unit of organ dysfunction scores to be used in the included studies can be different, thus we will calculate the standardised mean difference (SMD) to pool these data. As SMD is difficult to interpret, we will use the ratio of means for time to cessation of vasopressor therapy, and ICU length of stay in the sensitivity analysis.[26 27]

If organ dysfunction scores at 72-hour postrandomisation were not reported, we will extract the score at 96-hour postrandomisation. If the score at 96 hours was not reported, then we will use the score 48-hour postrandomisation.

Missing outcome data

Missing outcome data are sometimes imputed in the original trial report. The appropriateness of the imputation method will be considered in the risk of bias assessment. Participants with missing outcome data will be excluded from the analysis.

Data on potential effect modifiers

From each included study, we will extract data on the following: study intervention and population characteristics that may act as effect modifiers: industrial sponsorship, blinding of the personnel, vasopressor dependency of the study population.

Assessment of risk of bias in included studies

Two independent authors will assess the risk of bias with regard to the primary outcome of this review in the included studies using the RoB V.1.0 tool described in the Cochrane Collaboration Handbook as a reference guide.[28] Any disagreement will be resolved through discussion, or discussed with a third author, if necessary. We will evaluate the risk of bias in the following domains: generation of allocation sequence, allocation concealment, blinding of study personnel and participants, blinding of outcome assessor, attrition, selective outcome reporting and other domains (industrial sponsorship, fixed-size block randomisation in an unblinded study, baseline imbalance, inappropriate study deviation or cointervention, fraud). Where inadequate details regarding these characteristics of the trials are provided in the publications, we will contact the trial authors in order to obtain further information. Risk of bias in each study will be classified as follows:

1. Low risk of bias: none of the domains is rated as high risk of bias and allocation concealment was rated as low risk of bias, and three or less were rated as unclear risk.
2. 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.
3. High risk of bias: all other cases.

Data synthesis

Characteristics of included studies and information flow in the network

We will generate descriptive statistics for each trial, and study population characteristics across all eligible trials, describing the types of comparisons and clinical or methodological variables such as year of publication, age, sepsis or septic shock, organ dysfunction score, severity of critical illness, sponsorship and country. The available evidence will be presented in the network graph. The size of the nodes will show the total number of patients accumulated for each treatment, the breadth of the edges will be weighted according to the inverse of the variance of the direct summary effect, and the colour of each edge will represent risk of bias (low, moderate or high).

Measures of treatment effect

Relative treatment effects

We will estimate the pairwise relative treatment effects of the competing interventions using OR for dichotomous outcomes and mean difference (MD) or SMD for continuous outcomes. We chose the OR because the calculations to estimate the component-specific effects in component NMA are dependent on the mathematical features of the OR; in turn, the risk ratio (RR) is not suitable because it lacks symmetry. Furthermore, a methodological study has found possible bias in Cochrane random-effects meta-analysis using RR due to the restricted range of RR.[29] Results from the NMA will be presented as summary relative effect sizes for each possible pair of treatments.

Assessment of transitivity across treatment comparisons and NMA

Transitivity is a key assumption of NMA, and it can be seen as an extension of the clinical and methodological heterogeneity across comparisons. We will investigate the distribution of the possible effect modifiers mentioned above across treatment comparisons carefully. We assume that patients who fulfil the inclusion criteria for studies considered for this SR are potentially eligible for any of the interventions that we plan to compare. If the included studies are sufficiently similar with respect to the distribution of the effect modifiers, we will conduct a random-effects NMA to synthesise all evidence for each outcome and obtain a comprehensive ranking of all interventions. We will assume a single heterogeneity parameter for each network. We will present the summary ORs or (S)MD for all pairwise comparisons in a league table. We will also estimate the prediction intervals to assess how much the common heterogeneity affects the relative effect with respect to the extra uncertainty anticipated in a future study. We will compare the tau-squared with their empirical distributions.[30 31] We will obtain a treatment hierarchy using the surface under the cumulative ranking curve (SUCRA) and mean ranks. SUCRA can also be expressed as a percentage interpreted as the percentage of the efficacy of a treatment that would be ranked first without uncertainty.[32]

Component NMA

We will also employ a component NMA model, which is an extension of the standard NMA model.[33] We will differentiate between the effect of a component and the effect of combination therapies. We will assume additivity of component effects, that is, the total effect of each combination of interventions is assumed equal to the sum of effects of the included components. In this model, adding a component c to a composite intervention X will lead to an increase (or decrease) of the odds of the event or (S)MD by an amount only dependent on c, not on X. Then the component-specific incremental OR will be denoted by iOR_c, where $iOR_c = OR_{(X+c)vs(X)}$. A large iOR_c suggests that component c has a large impact on the outcome. Then the estimation of ORs between any two composite interventions will be calculated by combining the component-specific incremental ORs.[34] For example, $OR_{(HD-vitC+GC)vs(vitC+vitB1)} = (iOR_{HD-vitC} \times iOR_{GC}) / (iOR_{vitC} \times iOR_{vitB1})$. As the calculations are dependent on the mathematical features of the OR, we will report the result as the OR.

Assessment of inconsistency

The evaluation of transitivity will be supplemented with an evaluation of consistency with the statistical agreement between direct and indirect evidence. We will use local as well as global methods to evaluate consistency.[35] We will use a side-splitting approach to evaluate inconsistency within each pair-wise comparison as a local method and the design-by-treatment model as a global method to detect inconsistency in the network.

Sensitivity analysis

We will perform the following sensitivity analyses to evaluate the robustness of our findings.

1. Analysing only studies with low risk of bias.
2. All-cause mortality at the longest follow-up.
3. Analysing only studies published in 2010 or after.
4. Analysing time to cessation of vasopressor therapy and ICU length of stay as the ratio of means.

We will perform NMA in R V.3.5.1 using the netmeta package.[36]

Assessment of confidence in network estimates

We will assess the confidence of the network estimates of the primary outcomes using the CINeMA framework,[37] which characterises the confidence of a body of evidence on the basis of within-study bias, across-studies bias, imprecision, heterogeneity and inconsistency. We will use a web application CINeMA.[38]

Ethics and dissemination

This review does not require ethical approval. We will publish findings from this SR in a peer-reviewed scientific journal and present these at scientific conferences. Also, the findings will be disseminated through media where appropriate with layperson language for the purpose of knowledge translation. The dataset will be locked when the The VitamInC, hydrocorTisone and thiAMINe in patients with Septic shock (VITAMINS) trial completes

90-day follow-up, which is scheduled for October 2019. The dataset will be made available based on a reasonable request to the researchers.

Patient and public involvement

There was no patient or public involvement in the development of this manuscript.

Limitations

We acknowledge several limitations of the proposed review. First, as we plan to do meta-analysis using aggregated data, we can only classify study arms of vitamin C into three groups, that is, VHD-vit C, HD-vit C and vit-C, according to the dosage as reported by the investigators. If a fixed dose, that is, g/day, was used in a trial, the effect of the intravenous vitamin C might be different in patients with various weights. Second, we compare multiple interventions in this SR which might be likely to find statistical significance solely by chance. As there are no formal and satisfactory methods to account for the multiplicity in SR, the results should be cautiously interpreted.

Conclusions

In this SR and NMA, we will assess the effect of intravenous vitamin C, vitamin B_1 or glucocorticoid therapy and that of the combination therapy on mortality, the severity of organ dysfunction, the length of vasopressor therapy and ICU length of stay in patients with sepsis. The NMA will also address which component(s) of the combination therapy would contribute the most to the effect.

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Contributors TF, AC, NL, PJY and RB devised the study. TF drafted the protocol, will assist with the data collection and will draft the results and discussion. AC, TAF, GS, AAU, PJY and RB revised the protocol, assisted with study design and will help draft the final manuscript. AB, NL, AP, CS and YT revised the protocol and will carry out the data collection. TF will carry out the statistical analysis with the inputs from GS and will be the guarantor of the review. All authors gave final approval of the version to be published and agreed to be accountable for all aspects of this work.

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