Lessening **O**rgan Dysfunction with **VIT**amin C

A Multicentre Concealed-Allocation Parallel-Group Blinded Randomized Controlled Trial to Ascertain the Effect of High-Dose Intravenous Vitamin C Compared to Placebo on Mortality or Persistent Organ Dysfunction at 28 Days in Septic Intensive Care Unit Patients.

ClinicalTrials.gov: NCT03680274

Statistical Analysis Plan

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Lessening Organ dysfunction with VITamin C (LOVIT): statistical analysis plan

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Abstract

Background: Lessening Organ Dysfunction with VITamin C (LOVIT) is a blinded multicentre randomized clinical trial that compared high-dose intravenous vitamin C to placebo in patients admitted to the intensive care unit with proven or suspected infection as the main diagnosis and receiving a vasopressor.

Objective: To describe a pre-specified statistical analysis plan (SAP) for LOVIT, prior to unblinding and locking of the trial database.

Methods: The SAP was designed by the LOVIT principal investigators and statisticians and approved by the steering committee and coinvestigators. The SAP defines the primary and secondary outcomes and describes the planned primary, secondary, and subgroup analyses.

Results: The SAP includes a draft participant flow diagram, tables, and planned figures. The primary outcome is a composite of mortality and persistent organ dysfunction (receipt of mechanical ventilation, vasopressors or new renal replacement therapy) at 28 days, where day 1 is the day of randomization. All analyses will use a frequentist statistical framework. The analysis of the primary outcome will estimate the risk ratio and 95% confidence interval in a generalized linear mixed model with binomial distribution and log link and considering site as a random effect. We will perform a secondary analysis adjusting for pre-specified baseline clinical variables. Subgroup analyses will include age, sex, frailty, severity of illness, Sepsis-3 definition of septic shock, baseline ascorbic acid level, and COVID-19 status.

Conclusions: We have developed a SAP for the LOVIT trial and will adhere to it in the analysis phase.

Registration: ClinicalTrials.gov identifier: NCT03680274 (21 September 2018)

Introduction

Sepsis, defined as a dysregulated host immune response to infection that leads to organ dysfunction and death [1], is a major global public health concern, causing up to 5.3 million deaths per annum. Current sepsis management is focused on prompt antimicrobial therapy and organ-supportive care; numerous trials of interventions for immune dysregulation have not demonstrated benefit [2]. Vitamin C is an endogenous antioxidant with multiple actions, including scavenging of oxygen radicals, restoration of endothelial function, and synthesis of norepinephrine and vasopressin as a cofactor. The finding of low vitamin C levels in critical illness and its association with poor outcomes has led to randomized clinical trials (RCTs) of intravenous vitamin C [3], including in sepsis [4], with variable results that do not exclude clinically meaningful improvements in patient outcomes.

The **L**essening **O**rgan Dysfunction with **VIT**amin C (LOVIT) trial is the largest trial to evaluate high-dose intravenous vitamin C in adults with sepsis. This statistical analysis plan (SAP) was written before data collection was complete for the last adult enrolled in the trial and prior to database lock and unblinding of the study team.

Methods

Design

LOVIT is a multicentre, parallel-group, allocation-concealed, blinded (participants, clinicians, study personnel, members of the executive and steering committees, and data analysts) superiority RCT, registered on 21 September 2018 (ClinicalTrials.gov identifier: NCT03680274). The trial protocol has been published [5]; the final version (7.0) is dated 15 February 2021. The primary aim of LOVIT is to determine whether intravenous vitamin C, administered to adults with sepsis receiving a vasopressor, reduces the composite outcome of mortality and persistent organ dysfunction [6] at day 28, when

compared to placebo. Persistent organ dysfunction is defined as dependency on vasopressors, mechanical ventilation, or incident renal replacement therapy.

Sites

35 sites in Canada, New Zealand, and France.

Inclusion criteria

Patients were eligible for inclusion if they were:

1) at least 18 years old;
2) admitted to an intensive care unit (ICU) with proven or suspected infection as the main diagnosis; and
3) treated with a continuous intravenous vasopressor infusion (norepinephrine, epinephrine, vasopressin, dopamine, or phenylephrine [or metaraminol in New Zealand]) at the time of eligibility assessment and at randomization.

LOVIT was designed before the coronavirus disease 2019 (COVID-19) pandemic, but patients with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection who otherwise met eligibility criteria were eligible for the trial.

Exclusion criteria

Patients were excluded for any of the following reasons:

1) more than 24 hours since ICU admission;
2) known glucose-6-phosphate dehydrogenase (G6PD) deficiency;
3) pregnancy;
4) known allergy to vitamin C;
5) known kidney stones within the past 1 year;
6) received any intravenous vitamin C during current hospitalization, unless incorporated as part of parenteral nutrition;
7) expected death or withdrawal of life-sustaining treatments within 48 hours;

8) previously enrolled in this study (LOVIT);
9) enrolled in a trial for which co-enrollment was not possible (determined on a case-by-case basis by discussion with the other trial's principal investigators).

Randomization

Trial participants were randomized in a 1:1 ratio to vitamin C or matching placebo using permuted blocks of variable size, undisclosed to study personnel, and stratified by clinical site using a web-based randomization interface. Pharmacists and technicians preparing the study medication (vitamin C or placebo) at each participating site were unblinded.

Intervention

The experimental intervention was intravenous vitamin C, administered in bolus doses of 50 mg/kg actual body weight, given every 6 hours for 96 hours (i.e., 200 mg/kg/day and 16 doses in total), as long as the patient remained in the ICU. For patients weighing ≥150 kg, the weight was considered as 150 kg to calculate the dose. Each dose was administered over 30-60 minutes, except for participants >120 kg, for whom the infusion time was prolonged so that the rate does not exceed 100 mg/min. Participants in the control arm received 5% dextrose or normal saline in a volume to match the vitamin C. Placebo was infused over the same period as per the instructions for vitamin C and was identical in colour and other physical properties to vitamin C. Administration of open-label vitamin C in either group was not permitted and constituted a protocol violation.

Primary outcome

The primary outcome is a composite of death or persistent organ dysfunction (defined as dependency on vasopressors, mechanical ventilation, or new replacement therapy) at day 28 [6]. Mechanical ventilation refers to invasive ventilation only, and patients receiving chronic renal replacement therapy before the index hospitalization do not meet criteria for persistent organ dysfunction on the basis of ongoing renal replacement therapy. Note that Day 1 refers to the day of randomization.

Secondary outcomes

Efficacy outcomes include:

1) Persistent organ dysfunction-free days in the ICU, defined as the number of days alive and not dependent on vasopressors, mechanical ventilation, or new renal replacement therapy, up to day 28 and while in the ICU. Patients who die on or before day 28 will be assigned a value of -1 (modified from [7]). Any patient not receiving renal replacement therapy on a given day will be counted as renal replacement therapy-free for that day, even if renal replacement therapy is delivered on the day before or after this renal replacement therapy-free day. For patients on chronic renal replacement therapy before ICU admission, renal replacement after randomization will not be counted as an organ dysfunction. Patients discharged from the ICU to a hospital ward before day 28 and who receive renal replacement therapy after ICU discharge will not be counted as having persistent organ dysfunction after ICU discharge. Patients discharged from the study ICU to another hospital's ward or ICU before day 28 and not receiving these interventions at discharge will be assumed not to be receiving them at day 28 if specific information is unavailable. Similarly, patients discharged from the study ICU to another hospital's ICU before day 28, and receiving any of these interventions at discharge from the study ICU, will be assumed to be receiving them at day 28 if specific information is unavailable.
2) Mortality at 6 months;
3) Health-related quality of life (HRQoL) in 6-month survivors, as assessed using the five-level EuroQol five dimensions (EQ-5D-5L) [8] questionnaire. This scale evaluates mobility, personal care, usual activities, pain/discomfort, and anxiety/depression and categorizes each of these dimensions into five levels that range from no problems to extreme problems. Respondents also evaluate their overall health status using a 100-point scale;

4) Global tissue dysoxia assessed at days 1, 3, and 7, measured by serum lactate levels [9]. This is assessed using liquid chromatography coupled with tandem mass spectrometry;
5) Organ function (including renal function) assessed by the SOFA (sequential organ failure assessment) score [10] at days 1, 2, 3, 4, 7, 10, 14, and 28. The SOFA score on day 1 may have included physiological data obtained after administration of study medication;
6) Inflammation at days 1, 3, and 7, assessed by serum interleukin-1 beta, tumor necrosis factor-alpha, and C-reactive protein levels, measured by Luminex (Luminex Corp., Austin TX USA);
7) An infection biomarker at days 1, 3, and 7, measured by serum procalcitonin level [11] using an enzyme-linked immunosorbent assay;
8) Endothelial injury at days 1, 3, and 7, assessed by serum thrombomodulin [11] and angiopoietin-2 levels [12], measured by Luminex (Luminex Corp., Austin TX USA).

Biomarker outcomes were measured only in patients enrolled in Canada. We included day 1 measurements of biomarkers in the outcome list above for completeness, although day 1 samples were taken before administration of the first dose of study medication, and these samples therefore provided baseline measurements. Biomarker analyses were conducted in a central study laboratory; due to delays in obtaining assays to measure procalcitonin and C-reactive protein, analyses of those secondary outcomes may be delayed and reported after the primary publication.

Safety outcomes include:

9) Stage 3 acute kidney injury as defined by Kidney Disease-Improving Global Outcomes criteria [13] using either serum creatinine or urine output criteria, at any time during the ICU stay;
10) Acute hemolysis, ascertained until 12 hours after the last dose of study medication, defined as clinician judgment of hemolysis, as recorded in the chart, or a hemoglobin drop of at least 25 g/L within 24 hours of a dose of study medication and 2 of the following: reticulocyte count >2 times the upper limit of normal; haptoglobin less than the lower limit of normal; indirect (unconjugated)

bilirubin >2 times the upper limit of normal; or lactate dehydrogenase >2 times the upper limit of normal. Normal values are as defined at each participating centre's laboratory. Severe hemolysis is defined as hemoglobin <75 g/L, at least 2 of the above criteria and the requirement for transfusion of at least 2 units of packed red blood cells. As a secondary assessment of this acute hemolysis and of severe hemolysis, medical records of patients flagged as having hemolysis will be adjudicated by 2 blinded steering committee members, and any patient with hemolysis judged at least possibly related to study drug after adjudication will be counted.

11) Hypoglycemia, defined as a blood glucose level measured in the hospital core laboratory of less than 3.8 mmol/L. Vitamin C therapy may be associated with falsely elevated glycemic readings when certain point-of-care glucometers are used to measure blood glucose [14]. Because elevated glycemic values may prompt iatrogenic hypoglycemic episodes if insulin or oral hypoglycemic agents are administered, hypoglycemic events will be reported as a safety outcome.

After trial registration and publication of the trial protocol [5], we added a secondary outcome of mortality at 28 days, which is a component of the primary outcome. The trial registration reports 3 other outcomes (vitamin C volume of distribution, clearance, and plasma concentration that are only relevant for a pharmacokinetic sub-study, whose analysis plan will be reported separately.

Adverse events

Following Canadian recommendations for adverse event reporting in academic critical care trials [15], expected adverse events (death, stage 3 acute kidney injury, hemolysis, hypoglycemia), whether severe or not, are pre-specified trial outcomes and will not be reported separately as adverse events. Unexpected adverse events that are serious (i.e. fatal, life-threatening, prolonging hospital stay, resulting in persistent or significant disability or incapacity, or constituting an important medical event according to the local principal investigator) and considered by the local principal investigator to be at

least possibly related to trial procedures will be reported to the Coordinating Centre within 24 hours of becoming aware of the event.

Sample size

We determined a minimum sample size of 800 participants based on the following assumptions. We established that an absolute difference of 10% in the composite outcome of death or persistent organ dysfunction (15% to 25% relative risk reduction) would be plausible [16, 17] and sufficiently large to change practice. Based on recent clinical trials in a similar population [18], the risk of 28-day persistent organ dysfunction or mortality in the control arm was expected to be approximately 50%. By enrolling 385 evaluable patients per arm, the study would have 80% power to detect a 10% absolute risk reduction (from 50% to 40%, which corresponds to a 20% relative risk reduction). To account for consent withdrawal and loss to follow-up, we planned to enroll 400 patients per arm. Because of the subsequent COVID-19 pandemic, which started after LOVIT had commenced recruiting and constituted extenuating circumstances [19], the steering committee approved the inclusion of eligible patients in whom SARS-CoV-2 infection was the cause of sepsis. However, the total sample size was increased to ensure that the original planned sample size (n=800) of non-COVID-19 participants was reached.

Statistical analysis

Interim analyses

The independent Data and Safety Monitoring Committee (DSMC) reviewed data on all serious unexpected adverse events at least possibly related to study medication, in addition to hemolysis, stage 3 acute kidney injury, and hypoglycemia after enrollment of 250 and 530 patients. The statistical plan for the interim analyses was included in the DSMC charter, which was written before enrollment of the first patient in the trial, and included in the protocol [5]. In an unadjusted analysis using Chi-square or Fisher's exact test as appropriate, if the one-sided p-value had been <0.1 (in the direction of harm in the

vitamin C arm) for any of the 3 safety outcomes, an interim two-sided analysis of the primary outcome would have been conducted. The DSMC could also have requested an analysis of the primary outcome at any time. This analysis would have generated a conditional power for showing statistically significant efficacy (superiority of vitamin C) in the final analysis of the primary outcome, assuming that the group-specific event rates observed to date had remained the same in the total sample size. If the conditional power for efficacy had been <20%, in the context of a one-sided p <0.1 for any of the safety outcomes, then the DSMC could have recommended stopping the trial to the steering committee. The DSMC could have made a similar recommendation even if these exact thresholds had not been met, based on its interpretation of the balance between safety and efficacy. At the second interim analysis, the DSMC performed an analysis of 28-day mortality and could have recommended stopping the trial to the steering committee if two-sided p<0.001. This Haybittle-Peto stopping boundary only trivially inflates the overall type I error, so the a p-value of 0.05 will be used to declare statistical significance in the final analysis [20].

After both interim analyses, the DSMC recommended continuation of enrollment as planned.

Intention-to-treat principle

We will analyze data from participants in the group to which they were allocated irrespective of protocol adherence. If ineligible participants were randomized, we allow post-randomization exclusions only if they meet all the following conditions: 1) the information about ineligibility was available at randomization; 2) participants did not receive the assigned intervention; 3) blinding maintained; and 4) two members of the steering committee blinded to allocation agree that the participant was mistakenly randomized after review of information from medical records available at the time of randomization [21, 22]. Patients who withdraw consent for their follow-up data to be used will also be excluded from analyses.

Other principles

This RCT will be analyzed using a frequentist approach. All statistical tests will be 2-sided, and the overall type 1 error for the primary outcome will be 5% at a significance level of 0.05. We will not report p-values for secondary outcomes and analyses. All estimates of treatment effect will be reported with 95% confidence intervals (CI).

Categorical variables will be summarized with counts and percentages (based on the number of patients with data), and continuous variables will be reported as mean (standard deviation) or median (interquartile range) as appropriate.

The main LOVIT manuscript will include analyses of the primary outcome and all secondary efficacy and safety outcomes, except for procalcitonin and C-reactive protein, as noted above. An unadjusted and adjusted analysis of the primary outcome and of 28-day mortality will be reported (see below); analyses of all other secondary outcomes will be unadjusted for baseline covariates.

Secondary outcome analyses will be performed regardless of the result for the primary outcome and will be considered exploratory.

Subgroup analyses will be performed regardless of the result for the primary outcome.

Analyses will be conducted using SAS 9.4 (SAS Institute Inc., Cary, USA) and R 4.0.3 (R Foundation for Statistical Computing, Vienna, Austria).

Trial profile

The flow of patients through the trial will be shown in a figure, as recommended by CONSORT (Figure 1) [23]. The figure will show the number of patients who fulfilled eligibility criteria, the number randomized, and the number analysed for the primary outcome. Reasons for eligible patients not randomized and for exclusion after randomization will be given.

Baseline characteristics

Table 1 will display baseline characteristics in the entire trial population, and by allocated group. These characteristics will include demographics, comorbidities, location of suspected infection, severity of illness, organ support (mechanical ventilation, renal replacement therapy), and laboratory data.

Adherence to protocol

Protocol adherence will be defined by the administration of at least 90% of scheduled doses of study medication (vitamin C or placebo), until completion of treatment protocol or ICU discharge, whichever comes first, and off-protocol administration of intravenous vitamin C.

Analyses of the primary outcome

For the principal analysis, we will report the number and percentage of patients who die or have persistent organ dysfunction at day 28. We will estimate the risk ratio and 95%CI in a generalized linear mixed model with binomial distribution and log link and considering site as a random effect [24]. If this model does not converge, we will estimate the risk ratio using modified Poisson regression with small sample correction [25], and if that model also does not converge, we will estimate the odds ratio with logistic regression; both models will consider site as a random effect. We will use the same approach for the secondary analyses of the primary outcome and for analyses of binary secondary outcomes.

In secondary analyses of the primary outcome, we will adjust for prespecified baseline characteristics (age, sex, Acute Physiology and Chronic Health Evaluation [APACHE] II score [26], baseline receipt of corticosteroids, and time from ICU admission to randomization). Continuous adjustment variables will be modelled using restricted cubic splines with 4 knots to account for non-linear relationships with the log risk of the primary outcome. If more than 5% of the intention-to-treat population is excluded from this adjusted analysis because of missing baseline characteristics, we will impute missing data using

multiple imputation with fully conditional specification to obtain ten imputed datasets. The adjusted analysis will be performed on the imputed datasets, and the results will be pooled using Rubin's rules so that both within and between imputation variance are counted. We will assume APACHE II score is missing only if all its components are missing; otherwise, we will assume that a missing component has a normal value and calculate the APACHE II score accordingly.

For patients with missing data on the primary outcome or on the secondary outcome of 28-day mortality (for example, due to loss to follow-up), the principal and adjusted analyses will only include data on patients with outcome data. We will conduct a best case-worst case unadjusted sensitivity analysis, assuming first that all patients with missing data who received vitamin C did not have the outcome, whereas those in the placebo group did, and assuming second that the opposite states apply. If these analyses give discrepant results, namely statistically significant in one case but not the other, or both statistically significant but in opposite directions, then we will use multiple imputation with fully conditional specification to explore the impact of missing data [27].

Subgroup analyses

We will evaluate the effect of vitamin C on the primary outcome in subgroups defined at baseline by age (<65 vs. ≥65 years), sex (male vs. female), frailty (Clinical Frailty Scale 1-4 vs. ≥5 [28]), severity of illness (quartiles of predicted risk of death from baseline APACHE II score), Sepsis-3 [1] definition of septic shock (vasopressor infusion required to maintain a mean arterial pressure of 65 mmHg and lactate ≥2 mmol/L, vs. vasopressor need alone), and baseline ascorbic acid level (as quartiles). We hypothesize that vitamin C is more beneficial in elderly patients, in those with greater frailty and illness severity at baseline, those who meet strict criteria for septic shock, and in those with lower baseline ascorbic acid levels. In addition to the 6 subgroups pre-specified in our published protocol, we will assess for a subgroup effect based on COVID-19 status (positive test by polymerase chain reaction or rapid antigen

test at baseline, vs. negative), hypothesizing no difference in treatment effect. We will report interaction terms from the generalized linear mixed model (as used in the principal analysis) with treatment group, subgroup, and their interaction and display the results in a Forest plot. We will assess the credibility of any subgroup effect with interaction $p < 0.05$ using a published tool [29].

Analysis of secondary outcomes

Unless noted, analyses will not be adjusted for baseline characteristics or for site.

Analyses of clinical secondary outcomes will proceed as follows:

- Mortality at day 28. We will conduct a principal unadjusted analysis and secondary analysis adjusted for baseline characteristics and site according to the analysis plan for the primary outcome outlined above. We will also conduct a best case-worst case unadjusted sensitivity analysis to account for missing data, with multiple imputation for missing outcome data if these two sensitivity analyses differ (as for the primary outcome).
- 6-month mortality. We will conduct a principal analysis using a Cox proportional hazards model, with site as a random effect. We choose a Cox model because we record the data of death for decedents, and because differences in duration of survival are plausibly important over a 6-month time horizon. Patients lost to follow-up or who withdrew consent for follow-up will be censored at last follow-up time (expected to be at hospital discharge).
- 6-month HRQoL. In survivors with complete follow-up, we will report the mean or median for each dimension of the scale and for the self-reported overall health status in each group. Differences in means or medians will be reported, as appropriate.
- Persistent organ dysfunction-free days in ICU, up to day 28. Analysis will be rank-based, with death assigned as -1 (modified from [7]). We will display an empirical cumulative distribution function for each group and report the median, along with a difference in medians.

- SOFA scores at pre-specified time points: Results by randomized group at each time point will be summarized descriptively and displayed in a boxplot. For scores during the first 7 days, we will use a linear mixed model to account for repeated measures, with random intercept and time for each subject and random effect for site. Because day 1 SOFA may not be a true baseline value, it will not be used to model SOFA on subsequent days. For patients who died before day 7, we will impute the worst (highest) value, and for patients discharged alive before day 7, we will impute based on data available for patients discharged alive. We will conduct a likelihood ratio test between the empty model and the one with time, group, and their interaction and will conduct additional testing of the terms in the model only that test is statistically significant. For SOFA scores beyond day 7, we will report differences in means or medians because of the expected large proportion of patients with missing data due to death or discharge from the ICU.

For each biomarker outcome, results by randomized group at each time point will be summarized descriptively and displayed in boxplots. We will use constrained longitudinal data analysis [30] to analyze biomarker results. At each of day 3 and day 7, groups will be compared using a linear mixed model and adjusting for day 1 biomarker level, with random intercept for site and unstructured within-patient covariance. Biomarker data will be transformed if necessary to satisfy model assumptions.

For safety outcomes, we will report the number and percentage of each pre-specified safety outcome, and the number of unexpected serious adverse events and number of patients with an unexpected SAE, in each treatment group. Differences will be reported as risk ratios.

Tables and figures

Draft tables and figures for the main manuscript are displayed at the end of the text, and planned additional tables and figures are described in Appendix 1.

<u>Funding, registration, and ethical approval</u>

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LOVIT was conducted with the support of the Canadian Critical Care Trials Group. The protocol has been approved by the Comité d'éthique de la recherche du Centre intégré universitaire de santé et de services sociaux de l'Estrie – Centre hospitalier universitaire de Sherbrooke (reference MP-31-2019-2945) and at each participating site. LOVIT is registered on ClinicalTrials.gov (NCT03680274; 21 September 2018).

Results

As of 17 January 2022, all patients completed recruitment in the trial. Follow-up at 6 months is anticipated to be available by the end of January 2022, with analyses to follow.

Discussion

LOVIT is a methodologically rigorous RCT of intravenous vitamin C monotherapy in critically ill patients with sepsis. The statistical analysis plan will guide the analyses of this trial.

Competing interests

The authors declare that they have no competing interests.

Acknowledgements

The complete list of contributors to LOVIT is available in the Appendix.

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Figure legend

Figure 1 Flow of patients through the trial

Table 1 Baseline characteristics

Characteristic	All patients	Vitamin C (n=)	Placebo (n=)
Age, years; mean (SD)			
Sex, n (%) Male Female			
Admission type,[1] n (%) Medical Emergency surgery Elective surgery			
APACHE II score; mean (SD)			
SOFA score;[2] mean (SD)			
Clinical Frailty Scale; mean (SD)			
Primary site of infection, n (%) Pulmonary Gastrointestinal/ intra-abdominal Blood Skin or soft tissue Urinary Central nervous system Other			
SARS-CoV-2 positive,[3] n (%)			
Lactate (mmol/L); mean (SD)			
Ascorbic acid level (µmol/L); mean (SD)			
Sepsis-3 definition met[4]			
Time from ICU admission to randomization, hours; mean (SD)			
Comorbidities, n (%) End-stage renal disease (chronic dialysis) Diabetes mellitus (type 1 or 2)			
Treatments, n (%) Corticosteroids Mechanical ventilation Renal replacement therapy			

APACHE, acute physiology and chronic health evaluation; SOFA, sequential organ failure assessment

[1] Patients with emergency or elective surgical admission came to the intensive care unit from the operating room or post-anaesthetic care unit.

[2] This SOFA score is recorded on day 1 (randomization) but may include components measured after the first dose of study medication.

[3] In these patients, coronavirus disease 2019 was suspected at baseline and subsequently confirmed, or confirmed at baseline.
[4] The Sepsis-3 definition includes the requirement for a vasopressor infusion and lactate $\geq$2 mmol/L.

Table 2 Primary and secondary outcomes

Primary Outcome	**Vitamin C**	**Placebo**	**Measure of association (95% CI)**
28-day mortality or POD, n (%)			
28-day mortality, n (%)			
POD at day 28, n (%)			
Secondary Outcomes			
POD-free days in ICU, up to day 28, n (%)			
6-month mortality, n (%)			
HRQoL (EQ-5D-5L score) at 6 months, mean (SD) EQ-VAS, mean (SD) Mobility Self-care Usual activities Pain/discomfort Anxiety/depression			
SOFA score; mean (SD) Day 2 Day 3 Day 4 Day 7 Day 10 Day 14 Day 28			
Safety endpoints			
Stage 3 acute kidney injury, n (%)			
Acute hemolysis, n (%) Adjudicated, n (%) Severe hemolysis, n (%) Adjudicated, n (%)			
Hypoglycemia, n (%)			
Serious adverse events, n (%)			

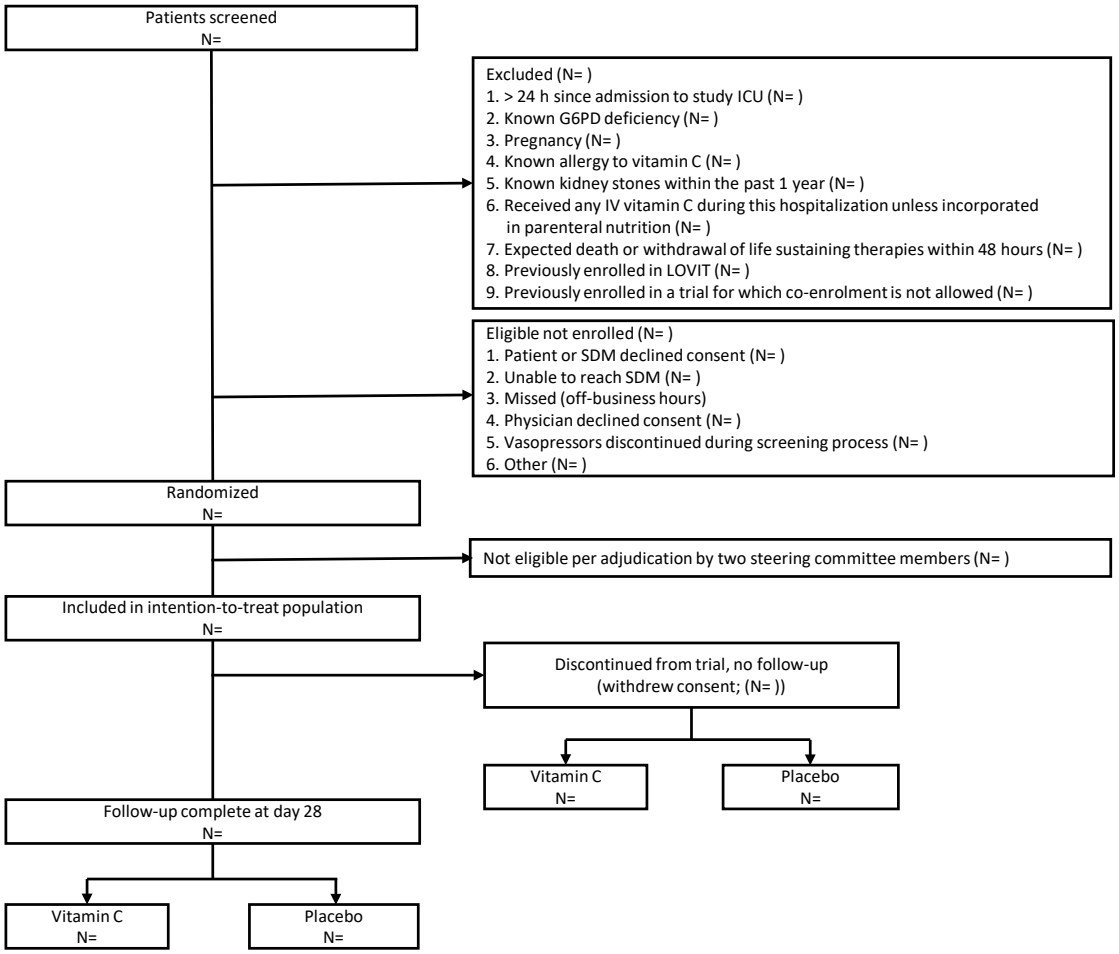
A p-value will only be reported for the primary outcome of 28-day mortality or POD.

HRQoL, health-related quality of life; POD, persistent organ dysfunction; SOFA, sequential organ failure assessment; VAS, visual assessment scale

Table 3 Additional figures planned for the main manuscript

Figure	Description
2	SOFA scores over days 1-7 in the vitamin C and placebo groups (displayed as a boxplot)
3	Subgroup analyses (displayed as a Forest plot)

Figure 1


Patients screened
N=
Excluded (N=)
1. > 24 h since admission to study ICU (N=)
2. Known G6PD deficiency (N=)
3. Pregnancy (N=)
4. Known allergy to vitamin C (N=)
5. Known kidney stones within the past 1 year (N=)
6. Received any IV vitamin C during this hospitalization unless incorporated in parenteral nutrition (N=)
7. Expected death or withdrawal of life sustaining therapies within 48 hours (N=)
8. Previously enrolled in LOVIT (N=)
9. Previously enrolled in a trial for which co-enrolment is not allowed (N=)
Eligible not enrolled (N=)
1. Patient or SDM declined consent (N=)
2. Unable to reach SDM (N=)
3. Missed (off-business hours)
4. Physician declined consent (N=)
5. Vasopressors discontinued during screening process (N=)
6. Other (N=)
Randomized
N=
Not eligible per adjudication by two steering committee members (N=)
Included in intention-to-treat population
N=
Discontinued from trial, no follow-up
(withdrew consent; (N=))
Vitamin C
N=
Placebo
N=
Follow-up complete at day 28
N=
Vitamin C
N=
Placebo
N=

Lessening Organ dysfunction with VITamin C (LOVIT): statistical analysis plan – appendix 1

Supplementary figures

Figure S1 Boxplot of SOFA scores over after day 7

Table S1 Baseline characteristics

Characteristic	All patients	Vitamin C (n=)	Placebo (n=)
Age, years; mean (SD)			
Sex; n (%) Male Female			
Height (cm); mean (SD)			
Weight (kg);[1] mean (SD)			
Body mass index (kg/m^2); mean (SD)			
Admission type, n (%) Medical Emergency surgery Elective surgery			
APACHE II score; mean (SD)			
SOFA score; mean (SD)[2]			
Clinical Frailty Scale; mean (SD)			
Primary site of infection; n (%) Pulmonary Gastrointestinal/ intra-abdominal Blood Skin or soft tissue Urinary Central nervous system Other			
SARS-CoV-2 positive;[3] n (%)			
Mean arterial pressure, mmHg; mean (SD)			
Lactate (mmol/L); mean (SD)			
Ascorbic acid level (µmol/L); mean (SD)			
Sepsis-3 definition met; n (%)[4]			
Time from ICU admission to randomization, hours; mean (SD)			
Time from hospital admission to randomization, hours; mean (SD)			
Transferred from ICU of another hospital, n (%) Time in other hospital ICU before admission to study ICU; mean (SD)			

Characteristic	All patients	Vitamin C (n=)	Placebo (n=)
Comorbidities,[5] n (%) Cardiac Supraventricular arrhythmia Angina or previous MI, CABG or PCI CHF class 1-3 CHF class 4 Ventricular arrhythmia Left ventricular ejection fraction (%), mean (SD) Vascular Known hypertension Cerebrovascular disease (TIA or stroke) Peripheral vascular disease or claudication Endocrine Diabetes (type 1 or 2) Renal Receiving chronic dialysis Baseline creatinine Gastrointestinal Moderate-to-severe liver disease Chronic lung disease Immunosuppression Neurologic Cognitive impairment/dementia			
Treatments, n (%) Corticosteroids,[6] n (%) Dexamethasone Prednisone Methylprednisolone Hydrocortisone Other Mechanical ventilation Renal replacement therapy			
Vasopressors (n, %) and dose (mean [SD]) Norepinephrine (μg/kg/min) Phenylephrine (μg/min) Epinephrine (μg/kg/min) Vasopressin (units/hr) Dopamine (μg/kg/min) Norepinephrine equivalents[7] (μg/kg/min) Metaraminol (mg/hr)			

APACHE, acute physiology and chronic health evaluation; CABG, coronary artery bypass grafting; CHF, congestive heart failure; ICU, intensive care unit; MI, myocardial infarction; PCI, percutaneous coronary intervention; SOFA, sequential organ failure assessment; TIA, transient ischemic attack

[1] Weight was measured when available and otherwise taken from the patient or family, or estimated.
[2] This SOFA score is recorded on day 1 (randomization) but may include components measured after the first dose of study medication.
[3] In these patients, coronavirus disease 2019 was suspected at baseline and subsequently tested and confirmed, or confirmed at baseline.
[4] The Sepsis-3 definition includes the requirement for a vasopressor infusion and lactate $\geq$2 mmol/L.
[5] Baseline creatinine refers to closest outpatient creatinine in the last 12 months, or lowest inpatient creatinine from the current hospitalization if no outpatient value available. Moderate-to-severe liver disease refers to Child's B or C cirrhosis and documented portal hypertension; episodes of past upper gastrointestinal bleeding attributed to portal hypertension; or prior episodes of hepatic failure/encephalopathy/coma. Chronic lung disease refers to chronic restrictive, obstructive, or vascular disease resulting in severe exercise restriction, i.e., unable to climb stairs or perform household duties; or documented chronic hypoxia, hypercapnia, secondary polycythemia, severe pulmonary hypertension (>40 mmHg), or respiratory dependency. Immunosuppression refers to malignancy requiring chemotherapy treatment in last 3 months; or neutropenia (absolute neutrophil count $<0.5 \times 10^9$/L); or receiving chronic immunosuppressive medications (azathioprime, cyclosporine, cyclophosphamde, tacrolimus, methotrexate, mycophenolate, anti-TNF agents, interleukin-2 agents) or transplantation (including stem cell) at any time; or HIV positive.
[6] Systemic (oral or IV) corticosteroids in the intensive care unit before randomization.
[7] Calculated according to the method in NEJM 2017; 377: 419–430.

Table S2 Protocol deviations

Type of deviation	All patients (n=)	Vitamin C (n=)	Placebo (n=)
	No. of deviations; No. (%) of patients with deviation		
Adherence			
Open-label administration of vitamin C			
Administration of ≥90% of scheduled doses of study medication			
Deviations			
First dose of study medication given >4 hrs after randomization			
≥1 dose of study medication missed			
Glucose monitoring to adjust insulin deviated from protocol			

Table S3 Cointerventions during the intensive care unit stay, including the day of randomization

Cointervention	All patients (n=)	Vitamin C (n=)	Placebo (n=)
Corticosteroids N (%) Days; mean (SD)			
Antimicrobials N (%) Days; mean (SD)			
Thiamine N (%) Days; mean (SD)			
Any sedation/analgesia infusion N (%) Days; mean (SD) Benzodiazepine infusion N (%) Days; mean (SD) Opioid infusion N (%) Days; mean (SD) Propofol infusion N (%) Days; mean (SD) Dexmedetomidine infusion N (%) Days; mean (SD)			
Any enteral or parenteral nutrition N (%) Days; mean (SD) Enteral nutrition N (%) Days; mean (SD) Parenteral nutrition N (%) Days; mean (SD) Oral intake N (%) Days; mean (SD)			
Insulin N (%) Days; mean (SD)			

Any blood product; n (%) Red blood cell; n (%) Frozen plasma, platelets, or cryoprecipitate; n (%) Albumin; n (%)			

Data were collected for the first 28 days, up to and including the day of discharge from the ICU. For each co-intervention, N refers to the number of patients that ever received it.

Table S4 Fluid balance during the first 7 days in the intensive care unit stay, including the day of randomization

	Day 1		Day 2		Day 3		Day 4		Day 5		Day 6		Day 7	
	Vit C	Placebo	Vit C	Placebo	Vit C	Placebo	Vit C	Placebo	Vit C	Placebo	Vit C	Placebo	Vit C	Placebo
Urine output, mL; mean (SD); n														
Fluid balance, mL; mean (SD); n														

Vit, vitamin

The mean hours of data on day 1, which included randomization to 23h59 on the same calendar day, was xx (SD xx).

Table S5 Life-sustaining therapies in the intensive care unit and additional outcomes

	Total (n=)	Vitamin C (n=)	Placebo (n =)
Life-sustaining therapy[1]			
Vasopressor infusion N (%) Days in survivors; mean [SD]; n Days in non-survivors; mean [SD]; n			
Invasive mechanical ventilation N (%) Days in survivors; mean [SD]; n Days in non-survivors; mean [SD]; n			
Non-invasive mechanical ventilation N (%) Days in survivors; mean [SD]; n Days in non-survivors; mean [SD]; n			
Renal replacement therapy N (%) Days in survivors; mean [SD]; n Days in non-survivors; mean [SD]; n			
Extracorporeal life support; n (%)			
Additional outcome			
Length of ICU stay, days (mean, SD; n) All patients ICU survivors ICU non-survivors			
Readmission to the ICU on or before 28 days, n (%)			
Length of hospital stay,[2] days (mean, SD; n) All patients Hospital survivors Hospital non-survivors			

ICU, intensive care unit.

[1] Data were collected for the first 28 days, up to and including the day of discharge from the ICU. For each life sustaining therapy, N refers to the number of patients that ever received it.
[2] Hospital stay is recorded for index stay in the study hospital only.

Table S6 Analyses of the primary outcome and of 28-day mortality

Model	Risk Ratio (95% confidence interval)
Principal analysis of primary outcome (GLMM, binomial distribution, random effect for site)	
Secondary analysis	
Adjusted for baseline characteristics	
Unadjusted, best case scenario Unadjusted, worst case scenario	
Principal analysis of 28-day mortality (GLMM, binomial distribution, random effect for site)	
Secondary analysis	
Adjusted for baseline characteristics	

GLMM, generalised linear mixed model

Best case-worst case unadjusted sensitivity analysis assumes first that all patients with missing data who received vitamin C did not have the outcome, whereas those in the placebo group did (best case), and assuming second that the opposite states apply (worst case)

Table S7 Credibility of subgroup assessments using ICEMAN tool

Subgroup	A priori	Prior evidence	Interaction test	Small number of effect modifiers	Cutpoint for continuous variable	Other	Overall
Age (<65 vs. ≥65 yr)							
Sex (male vs female)							
Frailty (Clinical Frailty Scale 1-4 vs. ≥5)							
Severity of illness (quartiles of predicted risk of death)							
Sepsis-3 criteria (vasopressor and and lactate ≥2 mmol/L, vs vasopressor alone)							
Baseline vitamin C level (quartile)[1]							
COVID-19 at baseline (present or not)							

The ICEMAN tool (Instrument to assess the Credibility of Effect Modification Analyses) is available at CMAJ 2020; 192: E901-6.

The questions are as follows:
1: Was the direction of the effect modification correctly hypothesized a priori?
2: Was the effect modification supported by prior evidence?
3: Does a test for interaction suggest that chance is an unlikely explanation of the apparent effect modification?
4: Did the authors test only a small number of effect modifiers or consider the number in their statistical analysis?
5: If the effect modifier is a continuous variable, were arbitrary cut points avoided?
6 Optional: Are there any additional considerations that may increase or decrease credibility?
7: How would you rate the overall credibility of the proposed effect modification?

[1] The p-value for the interaction between baseline vitamin C and treatment group was 0.xx; results for quartiles of vitamin C level are shown in Figure 3.

Table S8 Biomarker results

Biomarker	Day 1		Day 3		Day 7	
	Vitamin C (n=)	Placebo (n=)	Vitamin C (n=)	Placebo (n=)	Vitamin C (n=)	Placebo (n=)
Global tissue dysoxia Lactate (mmol/L)						
Inflammation IL-1ß (pg/ml) TNF-α (pg/ml)						
Endothelial injury TM (ng/ml) ANG-2 (pg/ml)						

Day 1 samples were collected before administration of study medication. Due to delays in obtaining assays to measure procalcitonin and C-reactive protein, analyses of these planned biomarkers may be delayed and reported after the primary publication.

ANG-2, Angiopoietin-2; IL-1ß= Interleukin-1 beta; TM= Thrombomodulin; TNF-α= Tumor necrosis factor-alpha.

Lessening Organ dysfunction with VITamin C (LOVIT): statistical analysis plan – appendix 2

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