ORIGINAL ARTICLE

A Pilot Feasibility Randomized Controlled Trial of Intravenous Vitamin C in Adults with Sepsis in the Intensive Care Unit: The Lessening Organ Dysfunction with Vitamin C-India (LOVIT-India) Trial

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Abstract

Background: The burden of sepsis is high in India and is associated with substantial morbidity and mortality. Vitamin C, an endogenous antioxidant, may improve patient outcomes.

Methods: This was a parallel-group pilot feasibility randomized controlled trial conducted at 2 intensive care units in India. Adult patients (≥18 years) with proven or suspected infection as the main diagnosis and needing a continuous intravenous vasopressor infusion were randomized to intravenous vitamin C (50 mg/kg every 6 hours for a maximum of 16 doses) or matching placebo. Primary outcomes were related to protocol adherence and feasibility (enrollment per month). The key secondary outcome was the composite of mortality or persistent organ dysfunction (POD) at day 28 after randomization.

Results: 60 patients were screened, 51 were eligible, 32 were randomized, and 30 were included in the analysis (randomized/eligible ratio: 0.63). The overall rate of enrollment was 1.5 patients per month. The median (IQR) age was 63.5 (51.0, 70.0) and 70.0% of the patients were male. In both arms, all patients received ≥90% of scheduled doses of the study drug. No patient received open-label vitamin C and there were no deviations from the glucose monitoring protocol. The composite outcome of mortality or POD at day 28 occurred in 56.3% (9/16) in the vitamin C arm as compared to 42.9% (6/14) in the placebo arm [RR: 1.31 (95% CI: 0.62, 2.76), $p = 0.47$].

Conclusion: In this pilot feasibility randomized controlled trial of vitamin C for adult patients with sepsis, protocol adherence was excellent and feasibility endpoints were met.

Trial registration: CTRI/2020/03/024371.

Keywords: Ascorbic acid, Developing countries, Randomized controlled trial, Sepsis.

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Highlights

- The burden of sepsis is high in India and is associated with substantial morbidity and mortality. Vitamin C, an endogenous antioxidant, may improve patient outcomes.
- We undertook a pilot randomized controlled trial to evaluate the feasibility of conducting a larger randomized controlled trial of vitamin C for adult patients with sepsis admitted to Indian intensive care units (ICUs).
- We enrolled 32 patients across 2 ICUs, demonstrated excellent protocol adherence and met trial feasibility endpoints.
- Mortality or POD at day 28 was 56.3% (9/16) in the vitamin C arm as compared to 42.9% (6/14) in the placebo arm [RR: 1.31 (95% CI: 0.62, 2.76), $p = 0.47$].

Introduction

Sepsis, defined as a dysregulated host immune response to infection that leads to organ dysfunction and death, is a major global public health concern, causing up to 11 million deaths per annum.[1,2] The epidemiology of sepsis in India is characterized by high burden and microbiology dominated by gram-negative and multi-drug resistant organisms.[3,4] Current sepsis management is

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focused on prompt antimicrobial therapy and organ-supportive care; numerous trials of interventions for immune dysregulation have not demonstrated benefit.[5]

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 controlled trials (RCTs) of intravenous vitamin C, including in sepsis, with variable results that, at the time this trial was designed, did not exclude clinically meaningful improvements in patient outcomes.[6–8]

The international lessening organ dysfunction with vitamin C (LOVIT) program of research encompasses several trials evaluating the role of vitamin C in sepsis: LOVIT [conducted in Canada, France, and New Zealand (NCT03680274)]; LOVIT-COVID, focused on patients with COVID-19 (NCT04401150); LOVIT-ARDS, focused on patients with septic acute respiratory distress syndrome (ARDS) in France (NCT04404387); and the current pilot feasibility LOVIT-India trial (CTRI/2020/03/024371).[9]

Given some of the well-known barriers to the conduct of clinical research and trials in India and other resource-limited settings, the primary objective of the LOVIT-India trial was to evaluate the feasibility of conducting a larger randomized controlled trial of vitamin C for adult patients with sepsis admitted to Indian intensive care units (ICUs). In addition, we evaluated the effect of vitamin C on several patient-centered secondary endpoints.[10]

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Conflict of interest: None

Methods

Trial Design and Approvals

LOVIT-India was a parallel-group pilot feasibility RCT conducted across 2 ICUs in Chennai, India. Both ICUs are tertiary care adult units admitting medical and surgical patients.

LOVIT-India was approved by the institutional ethics committee (AMH-011/03-19) and registered on the Clinical Trials Registry of India (CTRI/2020/03/024371). The trial is reported in accordance with the CONSORT extension for pilot and feasibility RCTs.[11]

Participants

We randomized adult patients (≥18 years of age) admitted to participating ICUs with proven or suspected infection as the main diagnosis and needing a continuous intravenous infusion of vasopressors (any dose of norepinephrine, epinephrine, vasopressin, dopamine, or phenylephrine). We excluded patients who had been admitted to ICU for >24 hours, pregnant women, those with known glucose-6-phosphate dehydrogenase deficiency, and those with a known allergy to vitamin C. The full list of exclusion criteria is available in the supplementary appendix (Page 2).

Informed consent was provided by patients or their legally approved representatives.

Interventions

In the experimental arm, intravenous vitamin C was administered in bolus doses of 50 mg/kg mixed in a 100 mL solution of normal saline (0.9% NaCl), over 30–60 minutes, every 6 hours for 96 hours (i.e. 200 mg/kg/day and a maximum of 16 doses in total). Patients in the control arm received equivalent volumes of normal saline (0.9% NaCl). Placebo was infused over 30–60 minutes as per the infusion instructions of vitamin C. The preparation of solutions administered to participants was the responsibility of the unblinded study pharmacist. Administration of open-label vitamin C in either group was not permitted and constituted a protocol violation. All other aspects of care, including the administration of glucocorticoids (including agents with mineralocorticoid effects) and thiamine, were at the discretion of the treating teams.

A potential risk of intravenous vitamin C is factitious hyperglycemia as recorded by capillary blood sugar point-of-care devices. This phenomenon does not occur with core lab assays, with specific glucometers whose measurements have been validated when serum ascorbic acid concentrations are high, or with many point-of-care blood gas machines. Accordingly, in keeping with other trials evaluating the same vitamin C regimen, for all participants receiving insulin or oral hypoglycemic agents, from the first dose of study medication to 36 hours after the last dose, glucose was measured either in the core lab or by the Nova Biomedical StatStrip glucometer (Nova Biomedical Ltd., Canada), which has been validated. Additional details of glucose monitoring are available in the supplementary appendix.

Outcomes

Primary Outcome

As this was a pilot feasibility trial, the primary outcomes were focused on protocol adherence and study feasibility. Protocol deviations included open-label administration of vitamin C and instances where no dose of the study drug was administered. Protocol adherence was measured by administration of ≥90% of scheduled doses, number of scheduled and administered doses, at least one scheduled dose of study medication missed, the first dose of scheduled medication given >4 hours after randomization, and any glucose monitoring deviations. Study feasibility was reported as the number of patients randomized per month per site (counting only months where screening was open) and the number of patients randomized as a proportion of the eligible patients.

The number of scheduled doses of vitamin C or placebo had a maximum value of 16, with values <16 if the patient died in or was discharged from the ICU or was transitioned to palliative care. Measures of adherence refer to the denominator of scheduled doses for each patient.

Secondary Outcomes

We also evaluated the impact of intravenous vitamin C on secondary outcomes: death or persistent organ dysfunction (POD) (defined as dependency on mechanical ventilation, new renal replacement therapy, or vasopressors) at day 28, mortality at day 28, POD at day 28, organ function assessed by the SOFA score (measured in the ICU on days 1, 2, 3, 4, 7, 10, 14, and 28, where day 1 was the day of randomization), occurrence of stage 3 acute kidney injury (AKI) (additional information in supplementary appendix), acute hemolysis, severe hemolysis (additional information in supplementary appendix), hypoglycemia, POD free days in the ICU up to day 28 (added after trial registration), health-related quality of life at 6 months among survivors, and lengths of stay in the ICU and hospital (added after trial registration).[12]

We telephoned patients or relatives 6 months after randomization to ascertain mortality at 6 months and health-related quality of life (HRQOL) among 6-month survivors.

Adverse Events

Following recommendations for adverse event reporting in academic critical care trials, expected adverse events (death, stage 3 AKI, hemolysis, hypoglycemia), whether severe or not, were prespecified trial outcomes and were not reported separately as adverse events.[13] Any unexpected adverse events that were 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 site investigator) and considered by the site investigator to be at least possibly related to trial procedures are reported.

Sample Size

Since the trial was designed as a pilot feasibility study and with the goal of understanding control and intervention group event rates for the primary outcome, LOVIT-India aimed to enroll between 25 and 100 patients. With an anticipated rate of adherence (defined as administration of ≥90% of scheduled doses) of 90%, the confidence interval (CI) would be 69–97% with enrollment of 25 patients and 82–95% with enrollment of 100 patients.

Randomization and Allocation Concealment

Using a continuously (24/7) available web randomization service (Randomize.net), trial participants were randomized in a 1:1 ratio to vitamin C or matching placebo. We used permuted blocks of undisclosed and variable size. Randomization was stratified by site.

Blinding

Intensive care unit clinical personnel, research personnel, participants, members of the steering committee, and the data analyst were blinded to the treatment allocation. Only the pharmacist who prepared the solution (vitamin C or placebo) was not blinded.

Analytical Methods

The statistical analysis plan (https://osf.io/xgu5d) was developed before database lock, analysis, and unblinding. All patients were analyzed as randomized in accordance with the intention-to-treat principle. Patients were analyzed by randomized group regardless of adherence with the exception of adverse events, which we report in an as-treated analysis. Patients who withdrew consent for their follow-up data to be used were included in analyses only to the extent permitted by their consent withdrawal; for example, if patients consented to baseline and follow-up data being used before a withdrawal of consent, that data was used.

Categorical variables are summarized with counts and percentages (based on the number of patients with data), and continuous variables are reported as means (SDs) or medians (IQRs) as appropriate. All tests are two-sided, with $p < 0.05$ taken as statistically significant. No subgroup analyses were planned. Analyses were performed using SAS v9.4 (SAS Institute Inc.) Estimates of treatment effects are reported with 95% CIs.

We used descriptive statistics to report feasibility and adherence outcomes. For feasibility, success was defined as enrolling >1 patient per site per month open for screening. For adherence, success was defined as at least 90% of patients receiving 90% of scheduled doses of investigational products and no more than 20% of patients having a glucose monitoring deviation.

For the key secondary outcome of the composite endpoint of POD or death at day 28, we compared the groups using log-binomial models and report risk ratios (RR) and 95% CI. We also report the number of patients meeting each part of the composite outcome (death or POD) separately. For 6-month HRQoL, in survivors with complete follow-up, we 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 and 95% CI are reported. SOFA scores by randomized group at each time point are summarized descriptively. For patients who die before day 7, we imputed the worst (highest) value, and for patients discharged alive before day 7, we imputed the value based on data available for these patients. We report differences in means or medians at each timepoint and 95% CI. Safety outcomes [stage 3 AKI, hemolysis, severe hemolysis, hypoglycemia, serious adverse events (SAEs)] are summarized as proportions and compared using Chi-square or Fisher's exact test as appropriate, and RR (95% CI) is reported. For POD-free days in the ICU up to day 28, analysis is rank-based, with death assigned as –1. We report the median in each group and compare them using quantile regression for differences in medians and 95% CI. Length of stay was considered separately in survivors and non-survivors, summarized by median in each group.

Additional details of the analyses can be found in the prespecified analysis plan, developed and published prior to database lock and unblinding (available here: https://osf.io/xgu5d).[14] Analyses of all secondary outcomes are unadjusted for multiplicity and should be considered hypothesis-generating.

Results

The trial was stopped on 13 February 2022 after preliminary analyses from LOVIT (Supplementary material Page 9) found an increased risk of death and POD in the vitamin C group.[9] From 12 May 2020 to 03 February 2022, we screened 60 patients, of whom 51 were eligible and 32 were randomized to receive either intravenous vitamin C or placebo. Enrollment was disrupted by the COVID-19 pandemic from May 2020 to December 2020, during which period screening was intermittent due to limited availability of research staff, and only 3 patients were randomized. Figure 1 depicts the flow of participants in the trial. After excluding 2 patients for whom consent was withdrawn prior to receipt of the study drug, 30 patients were included in the analysis. The last follow-up phone call was on the 10th of August 2022.

Table 1 describes the baseline characteristics of the patients enrolled in the trial. The median age was 66.0 (52.0, 70.0) years in the vitamin C arm and 60.0 (51.0, 70.0) in the placebo arm. 70.0%

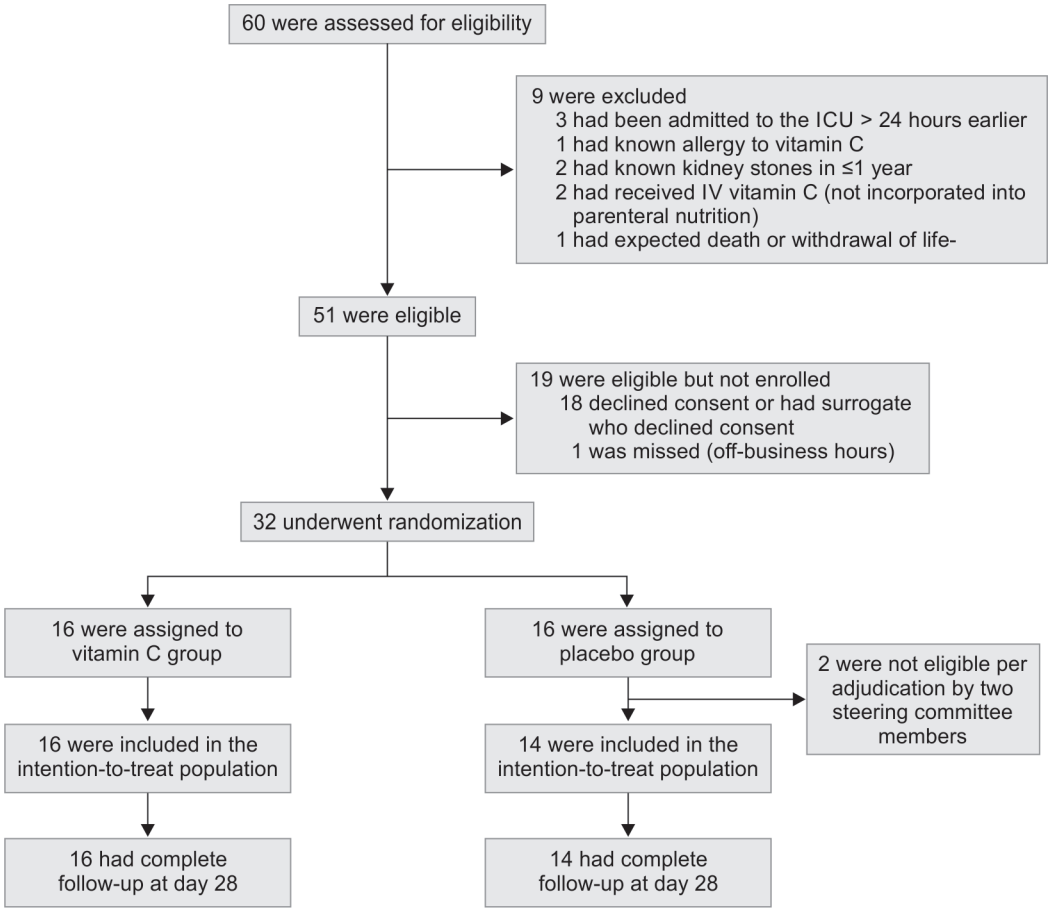

Fig. 1: CONSORT diagram

of enrolled patients were male and this was similar in both arms. The Acute Physiology and Chronic Health Evaluation II (APACHE II) score was lower in the vitamin C arm as compared to placebo [18.0 (13.5,22.5) vs 20.5 (15.0,24.0)]. However, the Sequential Organ Failure Assessment (SOFA) score on day 1 was higher in the vitamin C arm [11.0 (8.5, 13.5) vs 9.0 (7.0,13.0)]. The mean (SD) time from ICU admission to randomization was 16.2 (7.0) hours overall and was similar in both arms. In approximately 50% of the patients, the primary site of infection was blood. Other baseline characteristics were comparable.

Supplementary Table 1 provides the details of the microbiological diagnosis at baseline. Blood cultures were positive in 31.2% of patients in the vitamin C arm and 50.0% of patients in the placebo arm. 20% of the overall trial population tested positive for Dengue (NS1 antigen or IgM antibodies) or Scrub typhus (IgM antibodies).

Table 2 provides the results of protocol adherence and the feasibility outcomes. The overall rate of enrollment was 1.5 patients per month and 2.3 patients per month if we excluded the period of disruption resulting from the pandemic. The proportion of eligible patients that were randomized was 0.63. All patients received >90% of the scheduled doses and no patient received open-label vitamin C. One patient in the vitamin C arm received their first dose >4 hours after randomization. Glucose monitoring was performed as specified in the protocol in 100% of the patients in both arms.

Table 3 provides the results for the key secondary outcomes. Mortality or POD at day 28 was 56.3% in the vitamin C arm as compared to 42.9% in the placebo arm [RR: 1.31 (95% CI: 0.62,2.76), $p = 0.47$]. There were no episodes of acute or severe hemolysis, hypoglycemia, or other serious adverse events.

There were no differences in other secondary outcomes (Supplementary Table 2).

Discussion

In this pilot feasibility RCT, we demonstrated excellent protocol adherence and feasibility. This trial was not powered to detect differences in patient-important outcomes, but results numerically favored the placebo group, with fewer deaths, more POD-free days to day 28, and less AKI compared to vitamin C. There were no pre-specified safety events in either group and no serious adverse events were reported.

Our results are consistent with that of the parent LOVIT trial where patients randomized to the vitamin C arm had a higher risk of death or POD at day 28 (RR 1.21, 95% CI: 1.04–1.40).[9] In a systematic review that included the results of the LOVIT trial, when pooling trials at low risk of bias, moderate certainty evidence suggested that vitamin C had a higher risk of both in-hospital and 90-day mortality.[8] Based on these results, a recent rapid practice guideline has issued a conditional recommendation against the use of vitamin C in sepsis.[15]

Table 1: Baseline and day 1 characteristics

Variable	*Total (n = 30)*	*Vitamin C (n = 16)*	*Placebo (n = 14)*
Age, median (IQR)	63.5 (51.0, 70.0)	66.0 (52.0, 70.0)	60.0 (51.0, 70.0)
Sex male, *n* (%)	21 (70.0)	11 (68.8)	10 (71.4)
Type of admission medical, *n* (%)	30 (100.0)	16 (100.0)	14 (100.0)
Clinical frailty scale, median (IQR)	3.0 (3.0, 4.0)	3.0 (2.5, 4.0)	4.0 (3.0, 4.0)
Frail, CFS ≥5 (%)	4 (13.3)	2 (12.5)	2 (14.3)
APACHE II, median (IQR)	19.5 (14, 23)	18.0 (13.5, 22.5)	20.5 (15.0, 24.0)
SOFA score on day 1, median (IQR)	10.0 (8.0,13.0)	11.0 (8.5, 13.5)	9.0 (7.0, 13.0)
Time from ICU admission to randomization in hours, mean (SD)[a]	16.2 (7.0)	16.5 (7.3)	15.9 (6.8)
Primary site of infection, *n* (%)[b]			
Blood	14 (46.7)	7 (43.8)	7 (50.0)
Urine	9 (30.0)	5 (31.3)	4 (28.6)
Lungs/Respiratory	3 (10.0)	2 (12.5)	1 (7.1)
CNS/Brain	2 (6.7)	1 (6.3)	1 (7.1)
Intra-abdominal	5 (16.7)	3 (18.8)	2 (14.3)
Other	1 (3.3)	0 (0.0)	1 (7.1)
COVID-19, *n* (%)	2 (6.7)	2 (12.5)	0 (0.0)
Diabetes, *n* (%)	22 (73.3)	10 (62.5)	12 (85.7)
On chronic dialysis, *n* (%)	5 (16.7)	2 (12.5)	3 (21.4)
Treatments received on day 1, *n* (%)			
Kidney replacement therapy	12 (40.0)	8 (50.0)	4 (28.6)
Invasive ventilation	10 (33.3)	4 (25.0)	6 (42.9)
Noninvasive ventilation	8 (26.7)	6 (37.5)	2 (14.3)
Corticosteroids	18 (60.0)	9 (56.3)	9 (64.3)
Thiamine	9 (30.0)	6 (7.5)	3 (21.4)

[a]one patient was randomized 27 hours after ICU admission. [b]For any given patient, there could be more than one site of infection. [c]These treatments were delivered either at baseline or after randomization but on the day of randomization (study day 1). The numbers for kidney replacement therapy include those patients who were on chronic dialysis at baseline if they received this treatment on day 1. APACHE II, acute physiology and chronic health evaluation; CFS, clinical frailty sale; CNS, central nervous system; ICU, intensive care unit; IQR, interquartile range; SD, standard deviation; SOFA, sequential organ failure assessment

Table 2: Protocol adherence and feasibility

Outcome	*Total (n = 30)*	*Vitamin C (n = 16)*	*Placebo (n = 14)*
>90% of scheduled doses administered, *n* (%)	30 (100.0)	16 (100.0)	14 (100.0)
Number of doses, median (IQR)			
Scheduled	16.0 (13.0, 16.0)	16.0 (13.0, 16.0)	16.0 (13.0, 16.0)
Administered	16.0 (13.0, 16.0)	16.0 (13.0, 16.0)	16.0 (13.0, 16.0)
No dose given, *n* (%)	0 (0.0)	0 (0.0)	0 (0.0)
Open-label vitamin C, *n* (%)	0 (0.0)	0 (0.0)	0 (0.0)
First dose given >4 hours after randomization	1 (3.3)	1 (6.2)	0 (0.0)
Deviation from glucose monitoring protocol, *n* (%)	0 (0.0)	0 (0.0)	0 (0.0)

IQR, interquartile range

The exact mechanism of harm remains unclear. High doses of vitamin C can result in oxaluria and AKI. While the proportion of patients with AKI was higher in the vitamin C arm in our trial, this was not the case in the larger parent trial and did not explain the signal of harm. In the LOVIT trial, additional analyses of differences in biomarkers of tissue dysoxia, inflammation, and endothelial injury also did not identify a putative mechanism for harm.[9]

LOVIT included patients from high-income countries (HICs) with distinct patient, microbiological, and health system characteristics. LOVIT-India was initiated with the rationale that vitamin C may be more effective in India and other low- or middle-income countries (LMICs) due to a higher baseline risk of malnutrition, delays in presentation, and the higher proportion of gram-negative and 'tropical' infections and infections caused by multidrug resistant

Table 3: Secondary outcomes

Outcome	*Vitamin C (n = 16)*	*Placebo (n = 14)*	*Risk ratio (95% CI)*[a]
Mortality or POD at day 28, *n* (%)	9 (56.3%)	6 (42.9%)	1.31 (0.62, 2.76)
Mortality at 28 days	9 (56.3%)	6 (42.9%)	1.31 (0.62, 2.76)
POD at day 28	0 (0.0%)	0 (0.0%)	–
6-month mortality, *n* (%)	10 (62.5)	6 (42.9)	1.46 (0.71, 2.98)
Stage 3 acute kidney injury, *n* (%)[b]	9 (56.3)	6 (42.9)	1.31 (0.62, 2.76)
Acute and severe hemolysis, *n* (%)	0 (0.0)	0 (0.0)	–
Hypoglycemia, *n* (%)	0 (0.0)	0 (0.0)	–
Serious adverse events, *n* (%)	0 (0.0)	0 (0.0)	–

[a]Unadjusted. [b]The numerator excludes patients who were on chronic dialysis at baseline. CI, confidence interval; POD, persistent organ dysfunction

organisms.[3,4,16] Given the results of LOVIT-India and LOVIT, a larger trial of this vitamin C regimen in patients with sepsis in LMICs appears to be unjustified.

LOVIT-India was also set up to explore the broader feasibility of conducting RCTs for critically ill patients in India given barriers to the conduct of critical care trials.[10,17] While it is true that we enrolled a limited number of patients from 2 tertiary care centers in an urban setting, our results demonstrate that with the right combination of mentorship, capacity building, and equitable collaboration, methodologically robust trials can be set up to answer key questions of local and global relevance. In the recent past, there have been additional examples of such collaborative models.[18,19]

Strengths and Limitations

Our trial was conducted to the highest methodological standards. Patients, clinicians, and trial personnel were blinded to the intervention. We harmonized our trial protocol with the parent trial to enable future individual patient-level meta-analysis. In contrast to other vitamin C trials, we collected microbiological data. Our statistical analysis plan was developed and published prior to database lock and unblinding. Our trial also demonstrates an elegant model of international collaboration to answer questions of relevance for critically ill adults in HICs and LMICs.

There are important limitations. The trial was stopped prior to enrollment of the maximum planned sample size based on the results of the parent trial, and inferences on patient-important outcomes are weak. We did not collect data on baseline vitamin C levels or other biomarkers of relevance.

Conclusion

In this pilot feasibility RCT of vitamin C for adult patients with sepsis, we demonstrated protocol adherence and met feasibility endpoints.

Ethics Approval

LOVIT-India was approved by the institutional ethics committee (AMH-011/03-19) and patients or their legal representatives provided written informed consent.

Author Contributions

BKTV: Conceptualization, funding acquisition, methodology, project administration, writing-original draft, writing-review, and editing.

RV, YR, SM, DJ, PR, NR: Investigation, writing-review, and editing.

NKJA, FL: Conceptualization, methodology, project administration, writing-review, and editing.

RP: Methodology, formal analysis, visualization, writing-review, and editing.

MHM, JM, SS: Project administration, data curation, writing-review, and editing.

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Availability of Data and Materials: All data underlying the results are available within the manuscript. Additional data are available upon reasonable request. Deidentified patient data will be made available beginning 6 months after publication of the study and ending at 2 years. All requests for data sharing must be accompanied by a formal request, a study proposal with a clear statement of aims and hypotheses, and a statistical analysis plan and mailed to the corresponding author. Applications from investigators with suitable academic capability to conduct the proposed work will be given consideration. Any proposal will require approval from the ethics committee which approved the conduct of this trial prior to sharing any patient data. If a proposal is approved, a signed data transfer agreement will be required before data sharing. Reasonable personnel costs related to data transfer will be invoiced to the requesting investigators.

Clinical Trial Registration Number: CTRI/2020/03/024371.

Supplementary Material

All the supplementary materials are available online on the website of www.IJCCM.org.

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