Comparison of the effects of vitamin C and thiamine on refractory hypotension in patients with sepsis: A randomized controlled trial

Nandhini N, Deepak Malviya, Samiksha Parashar, Chandrakant Pandey, Soumya Sankar Nath, Manoj Tripathi

Department of Anesthesiology and Critical Care Medicine, Dr. Ram Manohar Lohia Institute of Medical Sciences, Lucknow, Uttar Pradesh, India

Address for correspondence: Dr. Soumya Sankar Nath, Department of Anaesthesiology and Critical Care Medicine, Dr. Ram Manohar Lohia Institute of Medical Sciences, Vibhuti Khand, Lucknow - 226 010, Uttar Pradesh, India. E-mail: soumynath2185@gmail.com

ABSTRACT

Background: The study aimed to compare the effect of thiamine and ascorbic acid (AA) on mortality, sequential organ failure assessment (SOFA) score, duration and dose of vasopressor support, and need for renal replacement therapy (RRT) in patients with septic shock with refractory hypotension.

Methods: Consenting adult patients with septic shock and refractory hypotension were included in this study. Patients were divided into three groups: Group A received 100 ml of balanced salt solution 8 hourly, Group B received 2 mg/kg of thiamine 8 hourly, Group C received 25 mg/kg of AA 8 hourly intravenous (IV) for 72 h. All patients received IV infusion of hydrocortisone 200 mg/day for 72 h. Serum lactate, dose and duration of vasopressor support, SOFA score, need for RRT and hospital mortality were analyzed.

Results: The SOFA Score was significantly lower in Group B than in Group A and C at 24, 48, and 72 h. Dosage of norepinephrine was lower in Group B at 66 h and after that, whereas in Groups A and C, it was comparable at all time points. Mortality in Group B was significantly lower but comparable in Groups A and C. The need for RRT was significantly lower in Group B (44%) compared to the control group (88%) but comparable in Group C (76%).

Conclusion: In patients with septic shock treated with hydrocortisone, co-treatment with thiamine led to earlier correction of organ dysfunction, reduced need for RRT, and improved mortality compared to patients treated with AA or balanced salt solution. The addition of AA did not yield measurable benefits beyond hydrocortisone alone.

Key Words: Ascorbic acid, hydrocortisone, lactate, septic shock, sequential organ failure assessment score, thiamine

INTRODUCTION

Sepsis, and more so, septic shock continues to result in unacceptable mortality among patients in intensive care units (ICU). The 30-day mortality in sepsis and septic shock patients was 24.39% and 34.7%, respectively.[1] A recent study from Japan reported that between 2010 and 2017, there was a significant increase in the number of sepsis patients (0.3%/year, from 2.9% to 4.9%) and deaths from sepsis (1.8/1000 inpatients/year).[2] Similar data were shared from France, where the incidence of sepsis and septic shock increased from 206 to 243 and 135–171/lakh
Moreover, the management of sepsis is all the more difficult because of the heterogeneity in risk factors, biomarkers, host response, and alteration in the endothelial activation, coagulation, and glucose and protein metabolism at play. The pathophysiology involves excessive immune activation and immunosuppression (marked by a drastic decline in monocyte human leucocyte antigen-DR in patients with poor outcomes following sepsis).

As a result, physicians started experimenting with metabolic resuscitation, wherein several pharmacological agents were supplemented, alone or in various combinations, to improve the mortality of patients with septic shock. Notable among these were hydrocortisone, thiamine, and ascorbic acid (AA). The hydrocortisone had been advocated in septic shock by Sepsis 3 guidelines backed by robust evidence of benefit as it reduces the dependence on inotropes.

Bauer et al. reported that mortality in patients with sepsis increases by 2.4% points for each point increase in sequential organ failure assessment (SOFA) score. Hence, there is an unmet need for improving organ dysfunction during sepsis management. The role of thiamine and AA, beneficial or otherwise, remains far from being established, as we find conflicting results.

Thiamine is an essential part of mitochondrial oxidative decarboxylation reactions, branched-chain amino acid metabolism, and the synthesis of adenosine triphosphate. Low thiamine levels are associated with elevated lactate with acidosis from underutilization of lactate by oxidation or conversion to glucose. In addition, thiamine ensures that nicotinamide adenine dinucleotide phosphate (NADPH) and glutathione are produced. The functions of NADPH include the regeneration of glutathione, anabolic processes including cholesterol and cellular membrane creation/maintenance, and free radical generation for immune reactions through NADPH oxidases. Glutathione generation is critical to protect from oxidative stress and free radical production, which is a significant contributing factor to the overall sequela of septic shock.

Thiamine deficiency occurs in about one-third of septic patients. Elevated lactate, acidosis, and hypotension occur in septic shock and thiamine deficiency. Subclinical deficiency likely augments the sepsis-induced thiamine depletion and may be due to reduced intake, impaired absorption, or increased urinary loss. Lack of adequate thiamine results in the failure of pyruvate to enter the tri-carboxylic acid cycle, thus preventing aerobic metabolism, which may lead to profound lactic acidosis (anaerobic metabolism).

AA performs essential functions such as antioxidant activity and regeneration, endothelial nitric oxide synthase/inducible nitric oxide synthase regulation, regulation of endothelium permeability, resolution of microvascular dysfunction, and endogenous catecholamine production through cofactor enzymatic activities as well as increased catecholamine receptor sensitivity by direct binding of the adrenergic receptors.

AA was found deficient in septic shock patients and its serum level correlated inversely with the incidence of multiple organ failure and directly with survival. Primates have lost the ability to synthesize AA due to the inability to catalyze the last step of production due to mutations in the L-gulono-γ-lactone oxidase gene. Humans are dependent on dietary sources. There is an upper limit of saturation of the leading transporter for AA in the gastrointestinal tract. When measured in sepsis and septic shock, levels are often depleted as splanchnic circulation decreases and utilization increases.

Depletion of AA in sepsis results from reducing plasma free iron, consumption by the scavenging of aqueous free radicals, and destruction of the oxidized form of AA, dehydroascorbic acid.

There is no conclusive literature on the comparative evaluation of the individual effects of thiamine and AA in septic shock. Hence, the present study was designed to evaluate the effect of thiamine and AA in patients with refractory hypotension in patients with septic shock. The trial’s primary objective was to study the impact of thiamine, AA, or a balanced salt solution on hospital mortality in patients with septic shock and refractory hypotension on systemic hydrocortisone therapy. The secondary objectives were to assess the impact of the aforementioned therapies on norepinephrine requirements, time to shock resolution, and the need for renal replacement therapy (RRT).
METHODS

This prospective, double-blind, randomized control study was conducted after approval from the institute’s ethical committee, from March 1, 2021 to August 30, 2021. The trial was registered prospectively at the Clinical Trial Registry of India (CTRI/2021/02/031043). Before inclusion in the study, written informed consent was obtained from the patient’s legal guardian. The manuscript adheres to the guidelines of CONSORT 2010 for randomized controlled trials [Figure 1]. All the enrolled patients were followed till discharge or death. All data were handled anonymously, and all information remained confidential. The study’s objectives were to evaluate the effect of thiamine and AA on mortality in patients with septic shock having refractory hypotension. Furthermore, we evaluated the effect on SOFA score, duration and dose of vasopressor support, need for RRT, and hemodynamic parameters in study groups.

Inclusion criteria
Adult patients (>18 years) with septic shock and refractory hypotension and those whose legitimate guardians had consented to participate in the study.

Exclusion criteria
Patients with glucose-6-phosphate-dehydrogenase deficiency, pulmonary hypertension, renal stones, iron overload, chronic alcoholism, pregnancy, antipsychotic medication, or with “Do Not Resuscitate” status were excluded from the study.

Sample size
From a previous study reported in the literature, the proportion of deaths in ICU in a group treated with thiamine and Vitamin-C was around 8% (πt) compared to 40% (πc) among control groups. Therefore, to perform a similar research study with a power of 80% and confidence limits of 95% (θ = 7.8), with an expected difference (δ) in the mortality rate of 32% between treatment group and control groups, sample size (m) was calculated using the formula

\[ M = \frac{\theta^2 (\pi_t (1-\pi_t) + \pi_c (1-\pi_c))}{\delta^2} \]

The estimated sample size per group would be a minimum of 24 in number. Hence, we have included 84 patients in our study with 28 patients enrolled in each group, data of 25 patients were analyzed in each group.

Method of blinding: the patient, their families, and the nursing staff were blinded to the group allocation throughout the process. After preparation, all the infusions looked identical and were prepared by a resident (NN). The syringes containing the infusions were coded. The treating physicians or the residents on duty were blinded to the infusion received by each patient. The data were collected by a different observer (SP), who was also blinded to the group to which the patient was allocated.

Septic shock was defined as sepsis requiring vasopressors to maintain mean arterial pressure (MAP) >65 mm Hg and lactate >2 mmol/L despite adequate fluid resuscitation.

Figure 1: CONSORT diagram
Refractory hypotension was defined as the inability to maintain mean MAP >65 mm Hg despite noradrenaline 0.5 mcg/kg/min and vasopressin 0.04 U/min for 1 h. Standard medical management was adopted in all study group patients. Following were the three groups:

**Control group (Group A)**
Patients received 100 ml of balanced salt solution given eight hourly for 72 h.

**Thiamine group (Group B)**
Patients received 2 mg/kg of intravenous (IV) thiamine in 100 ml of balanced salt solution 8 hourly for 72 h.

**Ascorbic acid group (Group C)**
Patients received 25 mg/kg of IV AA in 100 ml balanced salt solution 8 hourly for 72 h.

Since all the patients were in refractory shock, they were all mechanically ventilated. The patients' demographic data (age, gender, baseline diseases/cause of ICU admission), clinical characteristics (vital signs and hemodynamic parameters), and laboratory data were collected at baseline and every six-hourly interval for 72 h. The SOFA score was calculated daily until the study period (3 days) or mortality. The need for RRT was also determined. Mortality was defined as the primary outcome, and dose and duration of the vasopressor support, SOFA score and need for RRT were defined as secondary outcomes.

**Statistical analysis**
The statistical analysis was performed with IBM Statistical Package for the Social Sciences (SPSS) version 23 (Armonk, New York, USA) for all data analysis. First, all the quantitative variables were described using mean, median, and standard deviations. Next, all the categorical variables between the groups were compared using the Chi-square test with the Fisher’s exact test. Finally, the continuous variables between the groups (independent variables) were compared using the one-way Analysis of variance test. All the reported $P$ values were two-sided, and $P < 0.05$ were considered significant for all statistical analyses.

**RESULTS**

Ninety-eight patients admitted to the ICU were screened for eligibility. Fourteen of these patients were excluded (refusal to consent, history of renal stones, and chronic alcoholism). Hence, a total of 84 patients were enrolled in the study. Of these, complete data could not be collected in two patients (one each in groups A and B). Seven patients died before completing the study duration of 72 h (two each in Group A and B, and three patients in Group C). Hence, data of 75 patients (25 in each of the three groups) were analyzed [Figure 1]. Despite the dropouts, the calculated sample size could be fulfilled.

Table 1 compares demographic characteristics and associated comorbidities among different groups. We find that age, distribution of gender, and comorbidities are comparable among the groups. In addition, the baseline serum creatinine values (mg/dl) in Group A (1.31 ± 0.21), Group B (1.15 ± 0.23), and Group C (1.42 ± 0.18) were comparable.

Table 2 compares serum lactate of study Groups (B and C) to the control group (A). We found that the serum lactate was comparable at all periods among the three groups except at the 36th h when serum lactate was significantly lower in Group B than in the control group. It took 66 h in Group A, 60 h for Group B and Group C for the serum lactate to come down to normal levels.

Table 3 demonstrates the SOFA score of study Groups (B and C) compared to the control group (A). We found that the SOFA score was significantly lower at 24 h, 48 h, and 72 h in Group B compared to Group A. However, comparing the SOFA Score of Group C with Group A was comparable at 24, 48, and 72 h.

Table 4 compares norepinephrine requirements in the study group patients (Group B and C) compared to the control group (Group A). We found that the dosage of norepinephrine was lower in Group B at 66 h and after that, compared to Group A, whereas the dosage of norepinephrine in Group C was comparable to Group A at all time points.

Table 5 represents the death in the study groups patients. Comparison of mortality is depicted in Table 5. There was significantly lower mortality in Group B (28%) compared to Group A (60%) ($P = 0.021$). The mortality was also lower in Group B (28%) compared to Group C (48%) ($P = 0.039$), whereas the mortality was similar in Groups A and C.

Table 6 shows the comparison of the requirement of RRT between the groups. The requirement of RRT was significantly lower in Group B (22%) compared to Group A (88%), whereas it was comparable in Group A (88%) and C (76%).

**DISCUSSION**

To our knowledge, this is the first study that compared individually the efficacy of two inexpensive and readily available agents with a clinical safety profile in ameliorating the ill effects of septic shock. This study was also the first to examine the effects of thiamine and AA on the need for RRT in patients with septic shock.
We observed patients for 72 h, unlike previous studies, which restricted their period of observations to a much shorter time.

We did not find any difference in serum lactate levels among the study groups from the control group at any point except at 36 h when serum lactate was significantly lower in Group B (18.96 ± 4.52 mg/dl) compared to the control group (23.58 ± 4.59 mg/dl) [Table 2]. It took 66 h in Group A, 60 h for Group B and Group C for serum lactate to come down to normal levels. Similar to these, the dose of noradrenaline in Group B also became significantly lower from 66 h onward [Table 4]. Patients of Group B also had significantly lower mortality than the control group (*P = 0.04) [Table 5]. In a prospective observational study of 88 septic patients, Donnino et al. reported no significant benefit in time to shock reversal, illness severity, and mortality with thiamine administration. However, they showed significantly improved lactate clearance and lesser mortality among the subgroup of patients who had preexisting thiamine deficiency.[16] It is noteworthy that none of the patients received hydrocortisone.

Our study found that Group C showed no significant difference in serum lactate levels, the dosage of norepinephrine, or SOFA score from the control group at any point of time during the study period. [Tables 2-4] There were no significant differences in doses of vasopressor...

### Table 1: Comparison of demographic characteristics, associated comorbidities, sites of infection and baseline serum creatinine among different groups

| Time (h) | Group A (n = 25) | Group B (n = 25) | Group C (n = 25) | P |
|---|---|---|---|---|
| Baseline | 0.231 | 1.03 | 0.968 | 15 (60) |
| 1 | 0.23 | 1.023 | 1.000 | 13 (52) |
| 6 | 0.23 | 1.000 | 1.000 | 2 (8) |
| 12 | 0.23 | 1.023 | 1.000 | 3 (12) |
| 18 | 0.23 | 1.023 | 1.000 | 2 (8) |
| 24 | 0.23 | 1.023 | 1.000 | 3 (12) |
| 30 | 0.23 | 1.023 | 1.000 | 2 (8) |
| 36 | 0.23 | 1.023 | 1.000 | 3 (12) |
| 42 | 0.23 | 1.023 | 1.000 | 2 (8) |
| 48 | 0.23 | 1.023 | 1.000 | 3 (12) |
| 54 | 0.23 | 1.023 | 1.000 | 2 (8) |
| 60 | 0.23 | 1.023 | 1.000 | 3 (12) |
| 66 | 0.23 | 1.023 | 1.000 | 2 (8) |
| 72 | 0.23 | 1.023 | 1.000 | 3 (12) |

### Table 2: Comparison of serum lactate levels between Groups A at different periods

| Time (h) | Serum lactate (mg/dl), mean±SD | P | Serum lactate (mg/dl), mean±SD | P |
|---|---|---|---|---|
| Group A (n = 25) | Group B (n = 25) | Group C (n = 25) | Group A (n = 25) | Group B (n = 25) |
| Baseline | 23.03 ± 5.04 | 22.12 ± 5.47 | 1.023 | 23.03 ± 5.04 | 22.72 ± 4.64 | 1.023 |
| 6 | 21.62 ± 5.78 | 21.96 ± 5.71 | 1.03 | 21.62 ± 5.78 | 21.70 ± 4.61 | 1.023 |
| 12 | 23.15 ± 5.07 | 23.32 ± 6.08 | 0.967 | 23.15 ± 5.07 | 22.72 ± 4.64 | 1.021 |
| 18 | 23.03 ± 5.04 | 22.12 ± 5.47 | 0.898 | 23.03 ± 5.04 | 21.70 ± 4.61 | 0.968 |
| 24 | 22.88 ± 4.69 | 20.18 ± 4.32 | 0.623 | 22.88 ± 4.69 | 20.18 ± 3.95 | 0.231 |
| 30 | 19.74 ± 4.59 | 19.74 ± 4.59 | 0.053 | 19.74 ± 4.59 | 21.24 ± 5.71 | 0.120 |
| 36 | 19.86 ± 4.52 | 19.86 ± 4.52 | 0.041* | 19.86 ± 4.52 | 20.16 ± 6.20 | 0.111 |
| 42 | 19.31 ± 5.05 | 19.31 ± 5.05 | 0.061 | 19.31 ± 5.05 | 20.18 ± 5.17 | 0.123 |
| 48 | 20.12 ± 5.61 | 20.12 ± 5.61 | 0.111 | 20.12 ± 5.61 | 20.58 ± 5.10 | 0.111 |
| 54 | 19.12 ± 5.28 | 19.12 ± 5.28 | 0.089 | 19.12 ± 5.28 | 20.57 ± 4.82 | 0.112 |
| 60 | 18.55 ± 3.83 | 18.55 ± 3.83 | 0.102 | 18.55 ± 3.83 | 18.60 ± 4.31 | 1.00 |
| 66 | 18.79 ± 7.74 | 18.79 ± 7.74 | 0.72 | 18.79 ± 7.74 | 19.25 ± 6.08 | 1.00 |
| 72 | 17.86 ± 7.06 | 17.86 ± 7.06 | 0.88 | 17.86 ± 7.06 | 18.61 ± 5.75 | 1.102 |

### Table 3: Comparison of sequential organ failure assessment score between groups at different periods

| Time (h) | SOFA base | SOFA 24 | SOFA 48 | SOFA 72 |
|---|---|---|---|---|
| Group A | 12.20 ± 1.15 | 12.20 ± 1.15 | 11.28 ± 0.93 | 10.68 ± 0.80 |
| Group B | 12.20 ± 0.85 | 10.68 ± 0.85 | 9.40 ± 1.00 | 7.88 ± 1.20 |
| Group C | 12.20 ± 1.15 | 12.20 ± 1.15 | 11.28 ± 0.93 | 10.68 ± 0.80 |

*Significant. SOFA: Sequential organ failure assessment, SD: Standard deviation
The findings of our study are in contrast to the two previous studies, albeit with a tiny sample size, which examined the role of AA in septic shock. Fowler et al. compared the effect of AA (50 mg/kg/day or 200 mg/kg/day) with placebo in septic shock for 4 days, with only eight patients each in the study groups and reported that there was a rapid reduction in SOFA scores, significantly reduced biomarkers of inflammation (C-reactive protein and procalcitonin). The mean plasma level of AA (17.9 ± 2.4 μM), before starting supplementation, was much below the normal range (17.9 ± 2.4 μ). However, the same authors, 5 years later, in the double-blind multicentric CITRIS-ALI randomized controlled trial, compared 50 mg/kg of AA with placebo, failed to find any significant difference in SOFA scores, biomarkers of inflammation and vascular injury (C-reactive protein and thrombomodulin) in patients with acute respiratory distress syndrome and sepsis. Zabet et al. studied the effects of AA in 14 surgical patients of septic shock and found that AA supplementation resulted in significantly lower usage and duration of epinephrine. Furthermore, the 28-day mortality in the study group was lower. The length of ICU stay was similar, and there were no data on SOFA scores.

SOFA scores were calculated every 24 h, starting from baseline till the end of the study. Group B had a statistically significant SOFA score reduction than the control group (Group A), from 24 h until the end of the study period. Group B had a statistically significant SOFA score reduction than the control group. The high dose AA group exhibited significantly faster declines in the SOFA score over time than placebo (P < 0.01). A retrospective study by Marik et al. also reported that the SOFA scores declined in all treated patients, with none of them developing progressive organ failure. The change in SOFA score at 72-h from 24 h was 4.8 ± 2.4 in the treatment group compared with 0.9 ± 2.7 in the control group (P < 0.001).

In our study, the need for RRT was lesser in Group B (44%) compared to Group C (76%) and Group A (88%). The need for RRT was significantly lower in Group A (thiamine group) compared to the control group (P = 0.002) [Table 6]. The literature search revealed one study, which was, in fact, a post hoc analysis of a previous study that evaluated the effect of thiamine used in patients with septic shock, and found lower serum creatinine level and duration of epinephrine. Furthermore, the 28-day mortality in the study group was lower. The length of ICU stay was similar, and there were no data on SOFA scores.

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failed to demonstrate any beneficial effect on acute kidney injury incidence.[22]

We observed that Group B had significantly reduced mortality compared to Group A, whereas the mortality in Group C was comparable to the control group [Table 4]. The reduction in mortality rate observed in our study and corroborated by the findings of other studies could be because of the salutary effect of thiamine on the SOFA score and decreasing levels of serum lactate and requirement for vasopressor, indicating improvement in organ function [Table 3]. A positive correlation between increasing SOFA score and mortality was reported.[15] Very few studies evaluated the role of thiamine or AA individually on the course of septic shock. Donnino et al. reported decreased mortality in the subgroup of patients who had preexisting thiamine deficiency at the time of enrolment in the study.[16] In a systematic review, Moskowitz and Donnino found that the optimal measurement technique to assess clinically significant thiamine deficiency is yet to be determined; neither is there any point-of-care test to assess for thiamine deficiency.[23] Two factors need to be considered; first, thiamine deficiency is quite common in patients with sepsis, and, more so in patients with alcoholism, high dose diuretic exposure, malnourished state, hyperemesis syndrome, etc.; second, the features of thiamine deficiency are often very similar to that of septic shock-like persistent lactic acidosis. Hence, it was suggested that it might be prudent to supplement thiamine in septic shock patients with persistent lactic acidosis.[24]

We did not find any adverse effects with thiamine or AA, but Chang et al. had to terminate the study midway because of hypernatremia in the study group who received HAT.[22] Hypernatremia was possible because of the salt of AA, i.e., sodium ascorbate, which might lead to hypernatremia when used in high dosage.[24] Earlier also, hypernatremia had been ascribed to AA infusion.[25] Scholz et al. also mentioned that AA was associated with hypernatremia, hospital-acquired infections, hyperglycemia, gastrointestinal bleeding, and fluid overload in the systematic analysis.[26] Further, the meta-analysis failed to demonstrate any significant reduction in mortality compared to control.[26] Moreover, in patients receiving high dose AA, the point of care blood glucose measurements may yield erroneous results as the molecular structure of AA and glucose are somewhat similar.[27]

Among the studies that examined the role of HAT, there were conflicting results. Marik et al., in a retrospective study evaluating the role of HAT in patients with sepsis, reported that the hospital mortality rate was significantly reduced in the treatment group (8.5%) compared to the control group (40.4%).[17] Chang et al. compared HAT with normal saline administration in patients with septic shock and found that although there was an improvement in SOFA score at 72 h, there was no difference in 28 days mortality. They did not report on ICU mortality.[22] Fujii et al. compared HAT with hydrocortisone alone in a similar group of patients and found that the administration of HAT did not lead to either earlier resolution of septic shock or improve the duration of time alive or in vasopressor free days.[28] However, Iglesias et al. reported that the time to shock reversal was significantly reduced with HAT. However, there was no difference in ICU or hospital mortality, ICU and hospital length of stay, and ventilator-free days.[29] Hwang et al. compared the combination of AA and thiamine with normal saline and found no significant change in SOFA scores or mortality, although there was an improvement in thiamine and AA serum levels.[30] Half of the patients in each group received hydrocortisone. Contradictory findings of these studies had been blamed on erroneous study design, particularly the uncontrolled use of hydrocortisone, whose beneficial effect had already been established, and it would amount to unethical behavior to withhold it from the control group patients.[24] All patients in control or study groups received hydrocortisone as advised by Sepsis 3 guidelines for septic shock. Hence, the confounding effect of hydrocortisone was removed.

We need to appreciate that metabolic resuscitation with thiamine or Vitamin C or a combination of the two may buy time to control sepsis (source control of infection, broad-spectrum antibiotics, etc.).[24] Without adequate measures to control sepsis, metabolic resuscitation by any agent is unlikely to alter mortality in septic shock patients.

We understand that our study suffers from several limitations like small sample size, single centered study design, and limited study duration (72 h). Moreover, we did not measure baseline serum thiamine and AA levels and their correlation with the quantum of benefit by their supplementation.

**CONCLUSION**

From the findings of our study and the results of published literature, it may be safely concluded that thiamine supplementation, along with hydrocortisone, could result in earlier correction of organ dysfunction, reduce the need for RRT, mortality benefit in patients with septic shock and its usage may be advocated given the high incidence of its deficiency in septic shock. On the other hand, AA did not demonstrate any beneficial role and given its possible serious adverse effects may be withheld pending further large trials.

**Research quality and ethics**

This study was approved by the Institutional Review Board/Ethics Committee at Dr. Ram Manohar Lohia Institute of...
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Conflicts of interest
There are no conflicts of interest.

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