ORIGINAL ARTICLE

Evaluation of the Effects of a Combination of Vitamin C, Thiamine and Hydrocortisone vs Hydrocortisone Alone on ICU Outcome in Patients with Septic Shock: A Randomized Controlled Trial

Sachit Sharma[1], Hem R Paneru[2], Gentle S Shrestha[3], Pramesh S Shrestha[4], Subhash P Acharya[5]

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Abstract

Aims and background: Glucocorticoids, vitamin C and thiamine have important biological effects in patients with sepsis and septic shock. Multiple studies have demonstrated the beneficial role of a combination therapy of vitamin C, hydrocortisone and thiamine in patients with sepsis and septic shock in terms of mortality reduction, and increase in the number of days free of ventilators and vasopressors.

Materials and methods: Patients who had septic shock were assessed for eligibility after intensive care unit (ICU) admission. After randomization, the treatment group received a combination of vitamin C, thiamine and hydrocortisone for a duration of 96 hours (16 doses) and the control group received hydrocortisone for a duration till the patient was on vasopressors. The primary outcome assessed was ICU mortality, and the key secondary outcome was the duration free of vasopressor administration at the end of 7 days.

Results: A total of 86 patients were included in the study. Seventy percent of patients in the control group and 58 percent in the intervention group died during ICU stay. None of the primary and secondary outcomes were statistically significant.

Conclusion: The use of a combination of vitamin C, hydrocortisone and thiamine has no added benefits over the use of hydrocortisone alone in patients with septic shock.

Clinical significance: The results of this clinical trial shows that the use of a combination of vitamin C, hydrocortisone and thiamine in patients with septic shock is not useful and should not be a routine practice in critically ill septic patients.

Keywords: Hydrocortisone, Intensive care unit, Septic shock, Thiamine, Vasopressors, Vitamin C.

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Highlights

Glucocorticoids, vitamin C and thiamine have important biological effects in patients with sepsis and septic shock. The results of this clinical trial shows that the use of a combination of vitamin C, hydrocortisone and thiamine has no added benefits over the use of hydrocortisone alone in patients with septic shock.

Introduction

Sepsis is defined as a life-threatening organ dysfunction caused by a dysregulated host response to infection. Organ dysfunction can be identified as an acute change in the total sequential organ failure assessment (SOFA) score of more than or equal to 2 points subsequent to the infection. The baseline SOFA score can be assumed to be zero in patients not known to have pre-existing organ dysfunction. A SOFA score of more than or equal to 2 reflects an overall mortality risk of approximately 10% in a general hospital population with suspected infection. Even patients presenting with modest dysfunction can deteriorate further, emphasizing the seriousness of this condition and the need for prompt and appropriate intervention, if not already being instituted.[1]

Septic shock is a subset of sepsis in which underlying circulatory and cellular/metabolic abnormalities are profound enough to substantially increase mortality. Patients with septic shock can be identified with a clinical construct of sepsis with persisting hypotension requiring vasopressors to maintain mean arterial pressure (MAP) more than or equal to 65 mm Hg and having a serum lactate level >2 mmoL/L (18 mg/dL) despite adequate volume resuscitation. With these criteria, hospital mortality is in excess of 40%.[1]

Around 15–19 million cases of sepsis are encountered worldwide yearly, a vast majority of which occur in low-middle income countries.[2] With evolving diagnostic and management strategies, though the 28-day mortality from sepsis in high-income countries has come down to about 25%, the mortality rate due to septic shock is still as high as 50%.[3,4] The mortality rate from sepsis and septic shock in low-income countries approaches nearly 60%.[5]

[1–5]Department of Critical Care Medicine, Tribhuvan University Teaching Hospital, Institute of Medicine, Kathmandu, Bagmati, Nepal

Corresponding Author: Sachit Sharma, Department of Critical Care Medicine, Tribhuvan University Teaching Hospital, Institute of Medicine, Kathmandu, Bagmati, Nepal, Phone: +9852049450, e-mail: sachitrupakhetee@gmail.com

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Current management strategies for patients with sepsis include early aggressive fluid resuscitation, early appropriate antibiotics, hemodynamic support with vasopressors, and identifying and controlling infected sites.[6,7] Although outcomes have improved with the bundled deployment of these strategies,[8,9] mortality remains high at 20–30%.[10,11] Cost-effective and low-risk therapeutic approaches to reduce the morbidity and mortality of sepsis are needed.

The last three decades have seen numerous phase II and phase III clinical trials evaluating the effectiveness of novel pharmacologic agents and therapeutic interventions, among which activated protein C, statins, selenium, monoclonal anti-TNF alpha, granulocyte colony-stimulating factor (G-CSF), intravenous immunoglobulin (IVIG), etc., are a few to mention. These proposed treatment modalities have been tested in an attempt to improve the outcome of patients with severe sepsis and septic shock. All of these efforts ultimately failed to produce a novel pharmacologic agent that improved the outcome of sepsis. For this reason, the 32% absolute mortality reduction observed in a recent study of a combination therapy, including intravenous vitamin C (1.5 gm every 6 hours), thiamine (200 mg every 12 hours), and hydrocortisone (50 mg every 6 hours), has attracted significant attention and enthusiasm.[12] By contrast, the sobering experiences of hundreds of phases 2 and 3 clinical trials of promising pharmacological agents, none of which demonstrated reproducible benefits among patients with sepsis, have caused others to have a more reserved response.[13] Although a few well-designed, randomized controlled trials of the vitamin C, thiamine, and hydrocortisone regimen have not shown a promising effect of the combination, the reported beneficial effects are biologically plausible, and more randomized controlled trials are warranted to confirm these findings.

The current study therefore aims to evaluate the effect of a combination of vitamin C, hydrocortisone and thiamine on intensive care unit (ICU) outcome in patients with septic shock.

Materials and Methods

This was a randomized controlled trial with an allocation ratio of 1:1, conducted at a tertiary level hospital in Kathmandu, Nepal. There were no changes in the protocol after starting the trial.

Patients admitted to Tribhuvan University Teaching Hospital (TUTH) ICU with septic shock according to the sepsis-3 definition requiring vasopressors and duration of septic shock not more than 24 hours were included in the trial.[1] Participants receiving a continuous infusion of norepinephrine, epinephrine, vasopressin, dopamine, phenylephrine, or other vasopressor agent at any dose for more than 1 hour to maintain a mean arterial pressure of at least 65 mm Hg despite intravenous crystalloid resuscitation of at least 30 mL/kg were included in the study. Also, participants had a suspected or confirmed infection, as evidenced by the ordering of blood cultures and the administration of at least one antimicrobial agent.

After ethical approval from the institutional review committee, Critical Care Unit, and Department of Anesthesiology of TUTH, patients were assessed for eligibility. If found eligible, written informed consent was obtained from patient/legal guardian. Randomization was done using a computer-generated randomization sequence, and patients were allocated to either a treatment group or a control group in a ratio of 1:1. Allocation concealment was done using sealed envelopes containing the sequential numbers generated by the computer. The generation of sequential numbers using a computer and preparation of sealed envelopes were done by a trained staff who was not involved in the study. The sealed envelopes were kept in the ICU department room sequentially and in separate folders and were opened by the physician on duty once a patient meeting the eligibility criteria for enrolment was encountered. The participants and the care provider working on the floor were not blinded to the intervention given to patients. The principal investigator and the data analysis team were blinded to the allocation. The patient's clinical and demographic data were recorded which included age, sex, actual body weight, height, body mass index (BMI), date of ICU admission, diagnosis, co-morbidities, baseline investigation (lactate, creatinine, platelets, P/F ratio, total bilirubin), vitals [Respiratory rate (RR), heart rate (HR), blood pressure (BP), temperature (T), SpO_2] and Glasgow Coma Scale (GCS), baseline SOFA score and requirement of mechanical ventilation. Marik et al. in their study detected a mortality difference of 32% between groups of patients receiving vitamin C and patients not receiving the drug.[12] Taking their result as a reference, we calculated a sample size of 86 patients (43 patients in each group), to detect a mortality difference of 32% in the control and intervention groups with a study power of 90. The participants were enrolled till the pre-calculated sample size was met. Patients were excluded if they were receiving any one of vitamin C, thiamine or hydrocortisone before they were screened for eligibility. The baseline levels of thiamine and vitamin C to detect any pre-existing deficiency of the respective drugs was not performed, and it is one of the limitations of our study.

The patients were stabilized if unstable, cultures (blood culture from B/L peripheral veins, sputum culture and urine culture) were sent if not sent before and appropriate antibiotics were started if not started before. Ulcer prophylaxis, deep vein thrombosis (DVT) prophylaxis was started if there were no contraindications. The ventilator management was done according to the lung protective ventilation strategy as per acute respiratory distress syndrome (ARDS) Network protocol.[14] Sedatives and analgesics were administered as per ICU protocol. A Conservative fluid management approach was adopted as per the fluid and catheters treatment trial (FACTT) trial strategy.[15] Lung ultrasound, echo screening, and IVC diameter variability with respiration were screened by the on duty ICU physician. Treatment/control protocols were enforced after randomization within 24 hours of onset of septic shock, and drugs in the treatment and control groups were administered as described. The treatment group received a combination of intravenous vitamin C [1.5 gm every 6 hours for a maximum of 4 days (16 doses) or until ICU discharge or death if the patient didn't survive for 4 days after randomization], intravenous hydrocortisone (50 mg every 6 hours for a maximum of 4 days or until ICU discharge or death if the patient didn't survive for 4 days after randomization) and intravenous thiamine (100 mg every 6 hours for a maximum of 4 days or until ICU discharge or death if the patient didn't survive for 4 days after randomization). The vitamin C was administered as an infusion over 30–60 minutes and mixed in a 50 mL solution of either dextrose 5% in water (D5W) or normal saline. Intravenous thiamine was given in 50 mL of either D5W or normal saline and administered as a 30-minute infusion. The control group received intravenous hydrocortisone (50 mg IV every 6 hours till vasopressors were stopped, the patient was shifted out of the ICU or died while still on a vasopressor). Any immediate side effects (allergies, anaphylaxis) encountered after administration of above-mentioned drugs had to be promptly managed according to ICU protocols, and documentation was made in the proforma. Patients were followed up daily, and various parameters were recorded. The first parameter recorded was duration in hours free of vasopressors

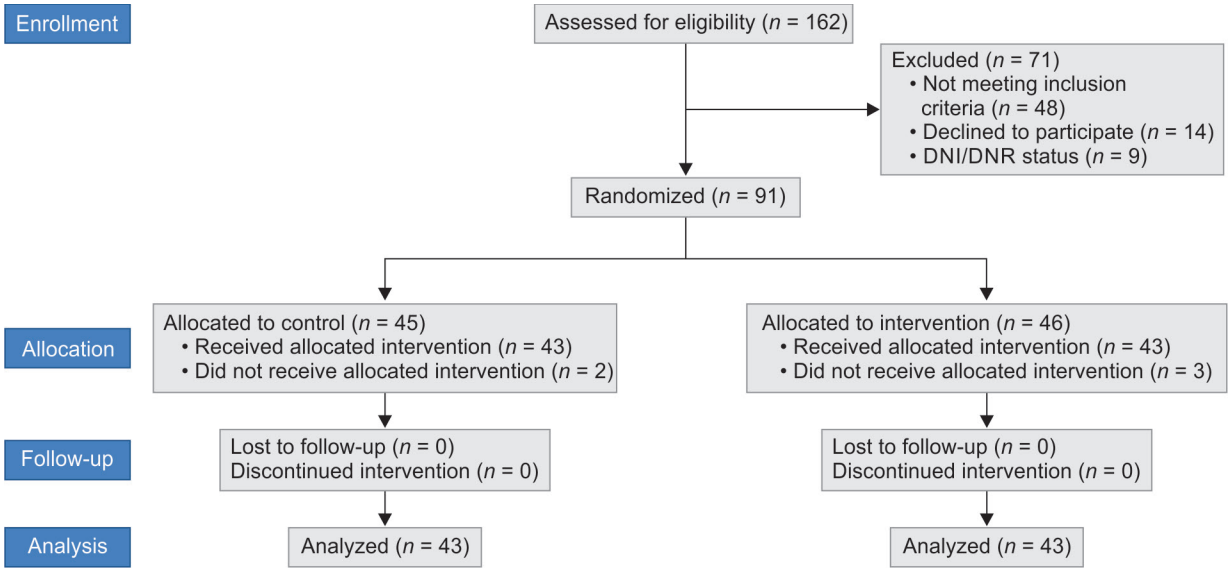

Fig. 1: Flowchart depicting patient enrolment, allocation, follow-up and analysis in control and intervention groups

till day seven. If a patient died while receiving vasopressor therapy during their initial septic shock episode, then this patient was assigned zero vasopressor free days. If the patient was again started on vasopressors after discontinuation, then the patient had to be on at least one vasopressor for at least 1 hour to label the patient as vasopressor dependent. The number of hours a patient didn't require vasopressor support per day was recorded. Daily requirement of vasopressor dosages (Noradrenaline equivalent) till day seven was also recorded. Injection adrenaline 0.1 µg was considered equivalent to injection noradrenaline 0.1 µg. Similarly, injection vasopressin 1.8 units was considered equivalent to injection noradrenaline 0.1 µg and injection dopamine/dobutamine 5 µg was considered equivalent to injection noradrenaline 0.1 µg. Another variable recorded daily was SOFA score after 3 days (72 hours) in which P/F ratio, total bilirubin, platelets, GCS and creatinine were recorded after 72 hours of randomization and SOFA score was hence calculated. Similarly, requirement of renal replacement therapy (RRT) till ICU stay/mortality and duration of mechanical ventilation (hours) were also recorded. The patient was then followed up till ICU stay/mortality and the duration of ICU stay and requirement of RRT during ICU stay was recorded. Vasopressors were gradually de-escalated, targeting a MAP of 65 mm Hg according to the sepsis-3 definition of septic shock.[1] Any changes in the hemodynamic parameters (HR, BP, T, SpO_2) or other features of an anaphylactic reaction (rashes, wheezing) after administration of each drug in the control or intervention groups were recorded and appropriate management was done by the physician on duty.

The primary outcome of the study was to compare the ICU mortality in patients with septic shock receiving a combination of vitamin C, thiamine and hydrocortisone with hydrocortisone alone. Similarly, the secondary outcomes were to compare the duration free of vasopressor administration at day 7, total vasopressor requirement at day 7, length of ICU stay, change in SOFA score after 3 days (72 hours), requirement of RRT during ICU stay and duration of mechanical ventilation in the intervention and control groups. There were no changes in trial outcomes after the trial commenced.

Data collection was done on a prepared sheet and entered in Microsoft Excel. Statistical analysis was done by using the statistical package for the social sciences (SPSS) software version 20.0 (SPSS Ltd, Chicago, IL, USA). Values are presented as mean ± standard deviation (SD) or frequency. Nominal categorical data were analyzed with a Chi-square test. For all determination, p-value < 0.05 (2-tailed) was considered statistically significant. Test of normality for continuous data was done using the Shapiro wilk test, and distribution was considered normal if the p-value was not significant ($p > 0.05$). Mann–Whitney U-test was applied for non-normally distributed continuous data, and independent samples t-test was applied for normally distributed continuous data.

Results

A total of 162 patients were assessed for eligibility in this study. Ninety-one patients were randomized, with 45 in the control group and 46 in the intervention group. Since 2 patients in the control group and 3 patients in the intervention group did not receive the allocated intervention, only 43 patients were analyzed for outcomes in each group. Recruitment was done from April 2020 till May 2021. The recruitment was stopped once the predefined sample size was met (Fig. 1).

The baseline characteristics of patients in the control and intervention were comparable and none of the variables were significantly different (Table 1).

The primary outcome was mortality during ICU stay. Seventy percent of patients in the control group didn't survive, in comparison to 58% in the intervention group. Though the number of survivors were numerically greater in the intervention group, the result was not statistically significant (p-value = 0.26) (Table 2).

The median duration free of vasopressors up to day 7 was 36 hours, vs 56 hours in the control and intervention groups. The result was not statistically significant, with a p-value of 0.15. Similarly, the median requirement of vasopressors up to day 7 was 22.40 µg/kg/min vs 14.85 µg/kg/min in the control and intervention groups respectively, which was not significant statistically with a p-value of 0.14. The median duration of mechanical ventilation during ICU stay was 168 hours vs 108 hours in the control and intervention groups respectively, which was again not significant statistically with a p-value of 0.08. The median length of ICU stay was 11 days, vs eight

Table 1: Baseline characteristics of control and intervention groups

Variable	*Control (n = 43)*	*Intervention (n = 43)*	*p-value*
Age (median, IQR) (years)	49 (17–84)	48 (18–87)	0.39
Sex (no. percent)			
Male	28 (65)	32 (74)	0.34
Female	15 (35)	11 (26)	0.34
Body mass index (median, IQR) (kg/m^2)	24 (19–35)	24 (17–30)	0.57
Mean arterial pressure (median, IQR) (mm Hg)	84 (52–105)	84 (54–105)	0.16
Heart rate (median, IQR) (bpm)	130 (100–160)	120 (87–150)	0.75
SpO_2 (median, IQR) (percent)	93 (82–99)	93 (80–100)	0.32
Temperature (median, IQR) (°C)	37.2 (36.1–39.3)	37.0 (35.2–38.8)	0.14
Respiratory rate (median, IQR) (cpm)	20 (14–32)	20 (12–30)	0.21
Glasgow Coma Scale (GCS) (median, IQR) (No.)	7 (2–15)	8 (2–15)	0.43
Lactate (mean, SD) (mmoL/L)	2.09 (1.18)	1.92 (1.46)	0.55
Creatinine (median, IQR) (µmol/L)	160 (40–478)	140 (44–572)	0.48
Platelet (median, IQR) (per mm^3)	140 (59–360)	131 (31–659)	0.91
P/F ratio (mean, SD) (mm Hg)	170.12 (71.50)	175.91 (83.97)	0.73
Total bilirubin (median, IQR) (µmol/L)	18 (8–111)	16 (7574)	0.17
Requirement of invasive mechanical ventilation (IMV) (no. percent)	39 (91)	39 (91)	1.0
Co-morbidities (no. percent)			
Hypertension (HTN)	9 (21)	12 (28)	0.47
Type II DM	4 (9)	7 (16)	0.33
Cardiovascular disease	0 (0)	3 (7)	0.07
Respiratory disease	2 (5)	1 (2)	0.55
Neurological disease	0 (0)	0 (0)	NA
Renal disease	0 (0)	1 (2)	0.31
Liver disease	4 (9)	1 (2)	0.16
Primary organ source of sepsis (no. percent)			
Central nervous system (CNS)	9 (21)	9 (21)	0.16
Respiratory	19 (45)	10 (23)	
Abdomen	11 (26)	12 (29)	
Renal	0	4 (9)	
Tropical disease	2 (4)	4 (9)	
Blood	0	2 (4)	
Skin and bones	2 (4)	2 (4)	

days in the control and intervention groups. This result was again statistically not significant, with a *p*-value of 0.08. Twelve patients in the control group and 8 patients in the intervention group required RRT during their ICU stay. This result was also not significant statistically, with a *p*-value of 0.30 (Table 3).

Table 2: ICU mortality in control and intervention groups

Outcome	*Control (n = 43)*	*Intervention (n = 43)*	*p-value (Chi-square)*
Intensive care unit mortality (no. percent)	30 (70)	25 (58)	0.26

The mean SOFA scores on admission and after 72 hours were compared in control and intervention groups, which were statistically not significant. Sequential organ failure assessment score decreased by 0.7 points in the control and 1.3 points in the intervention group after 72 hours. Numerically, the decrease in SOFA score after 72 hours was higher in the intervention group in comparison to the control group, but the result was not significant statistically (Table 4).

No significant adverse events attributable to any drug in the control and intervention groups were noted in the study.

Discussion

In this study, a total of 86 patients were analyzed for outcome, with 43 patients belonging to each of the control and intervention groups. Seventy percent of patients sustained mortality in the control group, in comparison to 58 percent in the intervention group. Though the mortality in the intervention group was numerically lower than in the control group, the result was not significant statistically (*p*-value = 0.26). Similarly, no significant differences were observed concerning vasopressor free days up to day 7, total requirement of vasopressors up to day 7, duration of mechanical ventilation, length of ICU stay, requirement of RRT and change in SOFA score after 72 hours between the control and intervention groups.

Similar to Marik et al.,[12] we aimed to determine the potential advantages of a combination of Vitamin C, Hydrocortisone and Thiamine over steroid alone in patients with septic shock. Several randomized controlled trials have been performed recently evaluating the effect of a combination of vitamin C, hydrocortisone and thiamine in patients with septic shock. Fujii et al. in 2020 published their study evaluating the effects of a combination of vitamin C, hydrocortisone and thiamine vs hydrocortisone alone in patients with septic shock.[16] In their study, the time alive and free of vasopressors was not statistically different between the two groups after 7 days of randomization, which was similar to our study. Their study also found no difference in mortality at 28 days and 90 days between the intervention and control groups. The dosage of drugs used in their study was similar to ours. In another study by Sevransky et al., the outcome variable compared was mortality before ICU discharge and mortality at 180 days in septic patients receiving a combination of vitamin C, hydrocortisone and thiamine vs placebo.[17] Both of these variables were found to have no statistical difference between the control and intervention groups, which was again a finding similar to ours. The dosage of drugs used in the intervention group was again similar to ours. The results of our study were remarkably different than those of Marik et al. in their retrospective before and after the study published in 2017.[12] It was noteworthy however that their study was not a randomized controlled trial and also had several limitations. A number of randomized controlled trials performed after their study have already demonstrated no difference in mortality

Table 3: Comparison of secondary outcomes in control and intervention groups

Outcome	*Control (n = 43)*	*Intervention (n = 43)*	*p-value*
Duration free of vasopressors up to day 7 (median, IQR) (hours)	36 (0–144)	56 (0–257)	0.15
Requirement of vasopressors up to day 7 (median, IQR) (µg/kg/min)	22.40 (1.6–100.8)	14.85 (0.1–71.1)	0.14
Duration of mechanical ventilation (median, IQR) (hrs)	168 (0–2016)	108 (0–840)	0.08
Length of ICU stay (median, IQR) (days)	11 (2–84)	8 (3–45)	0.08
Requirement of renal replacement therapy (no. percent)	12 (28)	8 (19)	0.30

Table 4: Change in SOFA score after 72 hours of ICU admission

Outcome	*Control (n = 43)*	*Intervention (n = 43)*	*p-value*
Sequential organ failure assessment score on admission (mean, SD)	11.47 (2.56)	11.70 (2.80)	0.69
Sequential organ failure assessment score on day 3(after 72 hours) (mean, SD)	10.77 (4.55)	10.40 (5.12)	0.72
Change in SOFA score after 72 hours (mean, SD)	–0.18 (4.55)	–1.27 (3.85)	0.23

or reduction in the duration of use of vasopressors in patients receiving a combination of vitamin C, hydrocortisone and thiamine vs hydrocortisone alone.[16–19]

There were six variables assessed as secondary outcomes in our study. These variables were duration free of vasopressors up to day 7, total requirement of vasopressors up to day 7, duration of mechanical ventilation during ICU stay, change in SOFA score after 72 hours of randomization, length of ICU stay and requirement of RRT during ICU stay. We took a cut off of 7 days to compare the duration free of vasopressors and total requirement of vasopressors between groups because earlier trials comparing hydrocortisone with placebo in patients with septic shock had demonstrated shock reversal well within the 7 days.[20,21] We therefore assumed that a 7-day cut off would be sufficient for the comparison. None of the secondary outcomes were significantly different between the control and intervention groups.

The results of our study demonstrated that a combination of vitamin C, hydrocortisone and thiamine had no additional benefits compared to hydrocortisone alone in patients with septic shock. We had used hydrocortisone in both the groups therefore, our results can also be interpreted in terms of the additional benefits of vitamin C, and thiamine in septic shock when added to a corticosteroid. No additional benefit of vitamin C, and thiamine was seen. Few studies in the past had already demonstrated no benefit of vitamin C, and thiamine when used alone in patients with septic shock.[22]

Our study also had a few limitations. Failure to follow the patients after ICU discharge till hospital discharge was a major limitation. The mortality rates between groups could have been different had we been able to follow the patients till hospital discharge. We therefore can only comment about the mortality at ICU discharge, which was not found to be significantly different between groups.

The results of the trial are largely generalizable, though the findings need to be reciprocated using trials of larger sample sizes.

Conclusion

The combination of vitamin C, hydrocortisone and thiamine has no additional benefits over steroid alone in patients with septic shock. Though there was numerical improvement in various parameters including ICU mortality, duration free of vasopressors up to day 7, total requirement of vasopressors up to day 7, total duration of mechanical ventilation during ICU stay, the requirement of RRT during ICU stay, change in SOFA score after 72 hours and length of ICU stay, none of the results met statistical significance.

Clinical Significance

The results of this clinical trial shows that the use of a combination of vitamin C, hydrocortisone and thiamine in patients with septic shock is not useful and should not be a routine practice in critically ill septic patients.

Orcid

Sachit Sharma https://orcid.org/0000-0002-7783-2361
Hem R Paneru https://orcid.org/0000-0002-3487-5388
Gentle S Shrestha https://orcid.org/0000-0003-0385-2340
Pramesh S Shrestha https://orcid.org/0000-0001-5890-0018
Subhash P Acharya https://orcid.org/0000-0003-1596-0496

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