Original Research Article

Effects of a high dose of vitamin C along with thiamine in critically-ill patients with septic shock: a randomized controlled trial

Running title: use of high dose vitamin c in septic shock

Abstract

Septic shock may occur in critically ill patients and despite antimicrobial treatment, it is associated with a high mortality rate. It is reasonable to look for new treatment modalities that might improve outcome. This is a randomized, double-blind control trial aiming at critically-ill septic patients in a tertiary hospital. Patients with quick sofa score of 2 and with organ dysfunction were included in this study. The intervention group received high doses of vitamin C at a dose of 50 mg/kg/four times daily along with thiamine at a dose of 200 mg/ twice daily) and the control group received normal saline for four days. The dose of vasopressors, procalcitonin and lactate clearance, and mean sequential organ failure assessment (SOFA) score were examined in the two groups. Patients were followed for 28 days. One hundred patients were allocated into two equal groups, and there was no difference between the two groups regarding baseline characteristics. Mean lactate concentration, SOFA score, days of antimicrobial therapy, and mortality at 28 days were similar between them. However, the mean procalcitonin concentration, and mean vasopressor treatment hours were significantly lower in the intervention group ($p<0.05$). Although Days of ICU stay were lower in the intervention group, It did not reach statistical significance. The results of this study showed that treatment with high dose vitamin C Reduces the vasopressor requirement without any effects on other parameters. Further studies with larger sample size are required for more generalizable results.

Keywords: Septic Shock, Vitamin C, Organ Failure

INTRODUCTION

Sepsis is a fatal complication of infections that causes physiologic, pathologic and biochemical dysfunction with a high mortality rate [1]. Different etiologic factors including bacterial, viral, parasites and fungal have been proposed for sepsis [2]. Host responses, innate immunity, coagulopathy, and inflammatory responses are involved in sepsis pathophysiology [3, 4]. The clinical features of sepsis are variable according to pathogens, infection sources, genetics and health status [3]. Respiratory and cardiovascular systems are affected more frequently [3]. Systemic inflammatory response syndrome (SIRS) and quick sequential organ failure assessment (qSOFA) were proposed for initial assessment of patients [2]. Previously Sepsis was defined as the occurrence of at least two of SIRS criteria along with confirmed or suspected infection [5]. The most recent revised definition has eliminated SIRS criteria and rely on sequential organ dysfunction as results of infections [1]. Recently, the third international consensus on sepsis definition recommend qSOFA for initial evaluation [1]. Quick SOFA defined as certain or suspected infection along with at least two of the following criteria: decline in level of consciousness, Systolic blood pressure < 100 mm Hg, respiratory rate > 22/min.

Septic shock is circulatory, cellular and metabolic dysfunctions in patients with sepsis. It is defined as mean arterial pressure ≤ 65mmHg and serum lactate levels ≥ 2 milimol despite adequate fluid resuscitation (1, 4).Different etiologic factors such as adrenal insufficiency, creation of reactive oxygen species, mitochondrial dysfunction, and vasopressin deficiency have been proposed for septic shock (6). Previous studies showed that antioxidant supplements may improve organ dysfunction, dose of vasopressors and mortality in septic shock [7-9].

Vitamin C is a water soluble acting as a free radical scavenger that may improve endothelial function, and micro- and macrovalcular functions [10]. In addition, a decrease in serum ascorbate levels has been reported in previous studies after intensive care admission [8, 11, 12]. Previous studies showed the safety and efficacy of vitamin C doses at 25-50 mg/kg four times daily [7, 9]. Increased oxalate concentration seen at daily doses of more than 10 grams [13]. Thiamine deficiency is prevalent in sepsis [14, 15]. Thiamine is a key vitamin in cellular metabolism and improve Krebs cycle, aerobic respiration, branched-chain amino acids [16]. Therefore, the aim

of the present study is to evaluate the possible role of high-dose vitamin C along with thiamine as compared with placebo in critically-ill patients with septic shock according to the recommendations of Society of Critical Care Medicine guidelines [17].

METHOD

Patients

This study was a randomized, single blind controlled trial conducted in a tertiary hospital in Kermanshah. Patients were allocated in two groups according to the random number generation software. Quick sofa was used for initial examination of patients. Patients with qSOFA of 2 and more were examined for possible sepsis. Other examinations such as Para-clinic data (serum creatinine, liver function test, white blood cells), chest X-ray, and cultures (sputum, blood, spinal fluid, and urine as indicated) were performed too.

Patients

One hundred Patients who were diagnosed with sepsis and signed the informed consent were included in the study. Pregnant patients, children and adolescents, and those with hypersensitivity to ascorbic acid, glucose-6 phosphate dehydrogenase deficiency, history of nephrolithiasis and immunosuppression were excluded from the study. Patients in the intervention group received high dose of vitamin C (50 mg/kg four times daily up to 6g/day) for 4 consecutive days along with thiamine 200 mg and patients in the placebo received normal saline. Other diagnostics and treatment modalities were similar for the two groups. All patients with septic shock received norepinephrine at the initial dosage of 4-20 micrograms/minute, to sustain mean arterial pressure of more than 65 mm Hg. Hydrocortisone at the daily dose of 200 mg was initiated at time of norepinephrine initiation.

Measurements

During the study, arterial oxygen pressure (PaO2) to the fraction of inspired oxygen (FiO2), systolic and diastolic hypotension, and renal and hepatic functions were tested daily. Sequential Organ Failure Assessment (SOFA) (18) and Acute Physiology and Chronic Health Evaluation

(APACHE II) were recorded (19). Acute Kidney Injury Network (AKIN) criteria were used for kidney function evaluation (20). All patients, if survived, were followed for 28 days.

The Mean concentration of lactate, procalcitonin at baseline and after 72 hours were recorded for all allocated patients. Additionally, Mean hours of vasopressor therapy, total days of mechanical ventilation, ICU stay, and mortality at 28 days were compared between the two groups.

Data Analysis

To perform the data analysis, we used the software SPSS-20. T-test was used for quantitative data and categorical data analysis was performed with Chi-squared test or fisher as appropriate. Wilcoxon and the Mann–Whitney-U tests were used.

RESULTS

During the study, 100 patients with mean age of 61.06 ± 16.02 years were included in the study. Demographic data are shown in table.1 where baseline charcteristics were similar in the two groups. Chronic obstructive pulmonary disease (COPD) was the main reason for the admission of patients, and other baseline diseases are demonstrated in table 1. Pneumonia was the main source for sepsis and septic shock, which was seen in 65% of all participants followed by intra-abdominal (15 %), and meningitis sources (10%) respectively. No definite source was detected in 10% of our patients. Mean SOFA score after 96 hours were similar between two groups (9.01 ± 3.92 vs. 10.67± 3.03, for intervention and control groups respectively, p=0.204). There was no significant difference between intervention and control groups regarding mortality after 28 days (15 % vs. 17 % respectively, p=0.36). In our study, mean hours of vasopressor therapy was 77.52 ± 21.5 and 111.5 ± 15.75 hours in intervention and control groups respectively (p=0.001).

The results of the present study did not show significant differences between the two groups regarding days of ICU stay 9.87 ± 8.32 vs. 12.67 ± 6.99 (p=0.32), and days

patients needed mechanical ventilation 6.67 ± 7.84 vs. 7.42 ± 6.23 (p=0.87). In addition, there was not any significant difference between the two groups regarding serum lactate after 72 hours 4.1±2.6 vs. 5.1±3.2 milimol (p=0.65). Although, a similar procalcitonin concentration was detected at baseline; however, mean serum procalcitonin concentration was significantly lower in the intervention group 2.21±1.5 vs. 4.13 ± 2.31 (p=0.001) after 72 hours. No significant adverse event was seen in our patients.

DISCUSSION

In the present study, we evaluated the safety and efficacy of vitamin C in critically-ill patients with septic shock. High doses of vitamin C was well tolerated and associated with lower duration of vasopressor requirement. As known, critically-ill patients are at a high risk of antioxidants concentration [21]. *Fowler et al* studied the safety of high dose (200mg/kg/ day) for four days, in septic shock, where treatment with high dose of vitamin C significantly increased plasma vitamin C concentrations without significant adverse events [8].

In our study, mean hours of vassopressr therapy was 77.52 ± 21.5 and 111.5 ± 15.75 hours in intervention and control groups respectively (p=0.001). This data is concordant with *Marik et al* [7]. They evaluated the effect of early use of high dose vitamin C along with thiamine and hydrocortisone can decrease the duration of vasopressor therapy (18.3 ± 9.8 vs. 54.9 ± 28.4 hours, respectively), organ dysfunction, and mortality. In addition, *zabet et al* reported lower mortality in patients who treated with high doses of vitamin C [9]. However, the mortality rate in our study didn't reduce in the intervention group. Results of our study is similar to *Litwak et al*. that showed treatment with marik's cocktail didn't significantly change outcomes (including mortality) in critically ill patients with septic shock compared with standard cares [22].

Mean duration of mechanical ventilation was not significantly lower in the intervention group. In the original study by marik and associates vitamin C, thiamine, and hydrorocortisone cocktail was associated with lower duration of mechanical ventilation [9]. Our data are consistent with *Shin et*

al. study that showed treatment with mentioned protocol versus control didn't affect duration of mechanical ventilation (5 (IQR, 3.0–15.0) vs. 5.0 (IQR, 3.0–10.0) days, p= 0.63) [23].

Duration of ICU stay was similar between the two groups. Shin et al and Litwak et al. that separately showed treatment with this protocol didn't decrease duration of ICU stay [22, 23]. However, Previous studies showed that treatment with vitamins E and C may decrease organ failure as measured by the SOFA score, hospital but not ICU stay in critically-ill patients [8, 22].

Patients treated with Thiamine and vitamin C had similar serum lactate clearance after 72 hours. Serum lactate levels and clearance may both be useful predictors of mortality in critically-ill patients [24]. Recently, a single center retrospective cohort study showed that treatment with a high dose of intravenous thiamine (1500 mg/day) within 24 hours is associated with an increase in lactate clearance and 28 days decrease mortality [25]. As mentioned in our study, only low dose of thiamine along with high dose of vitamin C was used.

Although mean procalcitonin was similar in the two groups at baseline, the intervention group had significantly lower procalcitonin concentration. It confirms the previous study by Fowler et al. showing that treatment with a high dose of vitamin C decreases inflammatory biomarkers, including c-reactive protein and procalcitonin concentration [8]. They demonstrated that vitamin C infusion may decrease procalcitonin concentration as high as 50%. Therefore, clinicians should interpret procacitonin concentration with caution.

Limitation

Our study had several limitations: Low sample size in both groups; Not being able to determine daily serum level of ascorbate. Although primary determined sample size size was 15 patients in each group, however, 100 patients were followed and included for the final analysis.

CONCLUSION

Results showed that treatment with a high dose vitamin C is well tolerated in critically-ill septic patients and may decrease total duration of vasopressor therapy and procalcitonin concentration without affecting the duration of ICU stay and one month mortality. Further studies with larger sample size is needed to confirm the possible role of high-dose vitamin C in similar populations.

Conflict of interest: The authors have declared that there is no conflict of interest.

ETHICAL APPROVAL

This study was approved by the Ethics Committee of Kermanshah University of Medical Sciences (IR.KUMS.REC.1396.341) and registered in IRCT (IRCT20130812014333N78).

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Table 1 Baseline characteristics of study population

	Intervention group	Placebo	P
Age (years)	56.21 ±13.62	61.07± 16.85	0.8
Female	55 (55%)	60(60%)	0.7
Body mass index (kg/m2)	25.75±2.29	25.43±2.43	0.43
Mean GFR (milliliter/min)	55±10	60±13	0.6
Mean SOFA score	10.2±2.5	9.8±3.8	0.32
Mean procalcitonin level (ng/ml)	1.25±1.6	1.99±1.56	0.146
Underling diseases / Reason for admission			0.75
COPD exacerbation	30	35	
Diabetes	20	15	
Guillan barre	2	0	
Chronic renal failure	17	20	
Hypertension	10	8	
Secondary Peritonintis	15	13	
Systemic lupus erythematosus	3	0	
Cerebrovascular accident	15	10	
Heart failure	10	7	
Epilepsy	3	1	

COPD: choronic obstructive pulmonary disease,

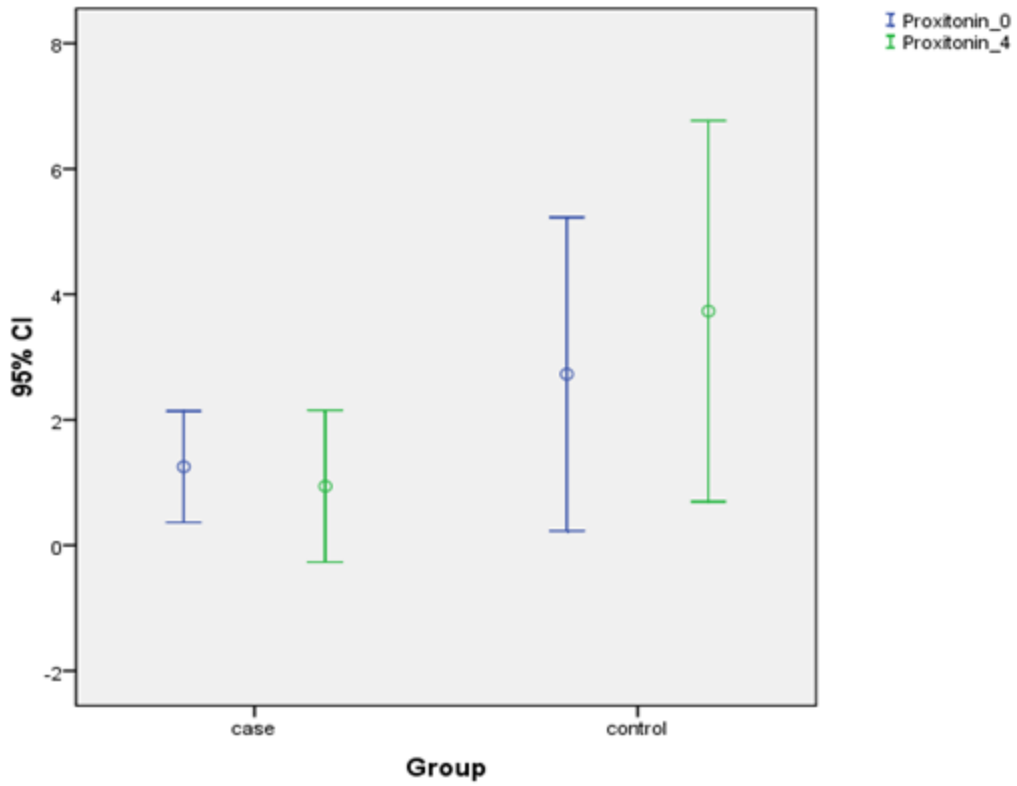

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Figure 1. Mean procalcitonin concentration before and end of intervention ($p<0.0001$)