e-ISSN: 0976-822X, p-ISSN:2961-6042

Available online on http://www.ijcpr.com/

International Journal of Current Pharmaceutical Review and Research 2023; 15(12); 822-826

Original Research Article

A Comparative Study between Vitamin C and Thiamine Vs Vitamin C and L Carnitine in Sepsis Patient: A Randomised Prospective Study

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Received: 12-09-2023 / Revised: 15-10-2023 / Accepted: 29-11-2023
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Conflict of interest: Nil

Abstract

Aim: The aim of the present study was to investigate the effects of high dose vitamin C, thiamine, L-carnitine supplementation on and compare which group is more effective in inflammatory mediators, oxidative stress, clinical outcomes, and the rate of mortality in ICU septic patients.

Methods: This study was a randomized controlled study conducted in the Department of Trauma and Emergency over a period of one year. Total 100-patients of sepsis, admitted in the intensive care unit of our hospital during this period were selected, as defined by the Sepsis 3 guidelines. We excluded patients with chronic kidney disease, chronic alcoholics and immunocompromised patients. The patients were divided 100 randomly into 2 groups of each and were followed through till discharge or death,

Results: The mean age of the subjects was 62.8 ± 16.4 and 56.4 ± 15.0 in group 1 and group 2 respectively. 51 (51%) were male and the mean APACHE3 score was 81.1 ± 23.6 and 56.9 ± 22.7 in group 1 and group 2 respectively. Liver failure was noticed in 5 patients in group 1 and in 7 patients in group 2. There was no statistically significant relationship between a patient's initial thiamine level and vitamin C level.

Conclusion: We found that mean ascorbic acid and thiamine levels were lower than normal range but that there was no relationship between these levels and outcomes, including 28 day mortality.

Keywords: vitamin C, thiamine, L-carnitine, supplementation

Introduction

Sepsis is a life-threatening condition caused by a dysregulated host response to infection and could lead to organ dysfunction. [1] Sepsis is a common disease in the intensive care unit, which is the leading cause of death from infection and major healthcare problems. The occurrence of sepsis was close to 50 million cases, while about 20% of all-cause deaths worldwide were sepsis-related. [2] A meta-analysis estimated the hospital mortality for sepsis to be close to 27%. [3] The mortality for sepsis can be as high as 46.7%, which is much higher than that in other critically ill patients. [2] Despite differences in medical expenditure between countries and regions [4], sepsis results in high healthcare costs due to its high incidence and the need for high-level medical care for critically ill individuals.

The total medical expenditures related to sepsis are the highest in the United States. [5] Early diagnosis and effective treatment of sepsis can reduce patients with severe sepsis, thereby reducing medical costs. [6] Vitamin C, also called ascorbic acid, can impact the expression of coagulation and proinflammatory genes. It can also regulate the immune system, maintain circulating cytokine homeostasis, and exhibit anti-inflammatory and antioxidant properties. [7] The level of vitamin C is often lower in patients with sepsis [8,9]; therefore, vitamin C

supplementation has become one of the measures to treat sepsis.

Being a water-soluble vitamin, vitamin C is generally considered to be safe even at high dosages. Although no clear guidelines or recommendations exist for the administration of vitamin C, it is still being used to manage these diseases, even in critically-ill patients. Mortality associated with sepsis and septic shock remains high though the disease, its prognosis, and management procedures are well established earlier. Intravenous fluid resuscitation and hemodynamic support, early administration of appropriate antibiotics, source control, and organ support from the mainstay of therapy. [10] Over the years, various therapeutic methods that include activated protein C, and vitamin C have been tested as adjuvant therapies to improve the outcomes. [11,12] However, these therapies failed to achieve any significant and meaningful outcome and their role in sepsis management remains ambiguous. [10]

The aim of the present study was to investigate the effects of high dose vitamin C, thiamine, L-carnitine supplementation on and compare which group is more effective in inflammatory mediators, oxidative stress, clinical outcomes, and the rate of mortality in ICU septic patients.

Materials and Methods

This study was a randomised controlled study conducted in the Department of Trauma and Emergency, Indira Gandhi Institute of Medical Sciences,Patna, Bihar, India over a period of one year. Total 100-patients of sepsis, admitted in the intensive care unit of our hospital during this period were selected, as defined by the Sepsis 3 guidelines. We excluded patients with chronic kidney disease, chronic alcoholics and immunocompromised patients. The patients were divided 100 randomly into 2 groups of each and were followed through till discharge or death. Apart from the standard treatment of sepsis, Group 1 received intravenous supplementation of VITAMIN C at a dose of 6 grams per day, as 2g, 3 times a day, for 5 days. Vitamin C was administered as an infusion over 30 to 60 minutes, mixed in a 100 ml. solution of either dextrose 5% in water (D5W) or normal saline. Intravenous supplementation of 200 milligrams of THIAMINE per day, 12 hourly, for 5 days. The intervention group 2 received three capsules of L-carnitine (each capsule contains 1000mgL-carnitine; totally 3000mg/day) for 5days and VITAMIN C at a dose of 6 grams, as 2 gm, 3 times a day, for 5 days. At beginning and end point of the study, inflammatory markers (CRP, erythrocytes sedimentation rate (ESR)), and clinical variables will be evaluated also. The mortality rate will be assessed within 28days of the beginning of the intervention. Blood samples were drawn on the day of admission from all 2 groups for routine investigations, to determine the SOFA score on Day 1. Day 6 SOFA scores of all patients as well as the difference between Day 6 and Day 1 SOFA scores (ASOFA score) were calculated. The outcome was recorded in terms of mortality in the various groups as well as the clinical improvement observed in terms of improvement in SOFA scores Eligibility criteria

Inclusion Criteria:

1. Septic patients who were hospitalized in the ICU. Sepsis was diagnosed using new definitions for sepsis and septic shock (Sepsis-3) by Surviving Sepsis Campaign International Guidelines for Management of Sepsis and Septic Shock: 2016.
2. Septic patients were recruited <24h after diagnosis
3. Age between 20 and 65years
4. Legal guardians wrote informed consent

Exclusion Criteria:

1. Patients who stay in hospital for 3days
2. Patients who receive parenteral nutritional support
3. Patients who receive enteral or oral nutrition at first but then transfer to parenteral nutrition due to the contraindication
4. Patients who would not be able to receive enteral nutrition or those who would not be able to receive enteral nutrition in the future because of incomplete resuscitation and hemodynamic instability or gastrointestinal disorders including nausea, persistent vomiting, ileus, intestinal obstruction, uncontrolled diarrhea (>500ml/day), high- output fistula (>500ml/day), and intestinal inaccessibility Patients undergoing dialysis, severe and progressive septic shock or sepsis, infection processes, DIC (diffuse intravascular coagulation), and any inflammatory interactions that interfere with intervention process were excluded.
5. Pregnancy
6. Patients who require frequent blood transfusions
7. Any unwanted side effects in patients after taking a supplement

Primary Outcome

1. Serum CRP, ESR, TLC, Procalcitonines as an inflammatory agent
2. Serum lactate dehydrogenase (LDH) as a marker of cell injury

Secondary Outcomes

1. Duration of hospitalization (days) and 28-day mortality rate

2. Differences in albumin (Alb), alanine aminotransferase (ALT), aspartate aminotransferase (AST), blood urea nitrogen (BUN), and creatinine in blood.

Statistical Analysis

Analyzing data was performed in the SPSS 20 (version) software. Normality was checked by Kolmogorov-Smirnov test. Qualitative data was reported as frequencies, normal continuous quantitative as mean (± SD) and median (IQR) for others. Differences within group were assessed with paired t-test and Wilcoxon rank-sum test. Between group differences also was assessed using independent t- test and Mann-Whitney U test. The significance level was considered $p<0.05$.

Results

Table 1: Demographic data

	Group 1	Group 2	p value
Age	62.8 ± 16.4	56.4 ± 15.0	0.052
Male	23 (46)	28 (56)	0.171
APACHE3	81.1 ± 23.6	56.9 ± 22.7	< 0.001
Thiamine (nml/L)	6.9 (3.9, 10.0)	5.9 (3.8, 8.7)	0.260
Vitamin C (mg/dL)	2.4 (1.1, 4.3)	2.3 (0.7, 4.1)	0.512
Liver failure	5 (10)	7 (14)	0.484

The mean age of the subjects was 62.8 ± 16.4 and 56.4 ± 15.0 in group 1 and group 2 respectively. 51 (51%) were male and the mean APACHE3 score was 81.1 ± 23.6 and 56.9 ± 22.7 in group 1 and group 2 respectively. Liver failure was noticed in 5 patients in group 1 and in 7 patients in group 2.

Table 2: Thiamine, vitamin C, and survival

	OR	95% CI	p value
Thiamine (nml/L)			
Survival to discharge	0.99	0.96–1.01	0.357
28 day survival	0.98	0.95–1.00	0.159
60 day survival	0.98	0.95–1.00	0.093
One year survival	0.98	0.95–1.00	0.144
Shock	1.00	0.97–1.04	0.790
Vitamin C (mg/dL)			
Survival to discharge	1.05	0.91–1.20	0.521
28 day survival	0.94	0.82–1.07	0.329
60 day survival	1.02	0.89–1.16	0.782
One year survival	0.93	0.84–1.03	0.168
Shock	1.02	0.94–1.12	0.595

There was no statistically significant relationship between a patient's initial thiamine level and vitamin C level.

Discussion

Sepsis, the syndrome of life-threatening dysregulated immune response to infectious pathogens, is both common and deadly. [1,13] Early screening and identification, aggressive resuscitation, and administration of appropriate antibiotics are associated with lower mortality in patients with severe sepsis. [14-16] However, the search for effective adjuvant therapies continues. Potential candidates include ascorbic acid (vitamin C) and thiamine (vitamin B1).

Clinical studies of vitamin C in the treatment of sepsis have shown mixed results on the mortality of patients. Some studies suggest that vitamin C could significantly reduce mortality in patients with sepsis [17-19], while others did not show any effect. [20,21] The use of vitamin C in the treatment of sepsis is controversial. There have been many high-quality randomized controlled studies on the treatment of sepsis with vitamin C in the last two years. [22-23] The mean age of the subjects was 62.8 ± 16.4 and 56.4 ± 15.0 in group 1 and group 2 respectively. 51 (51%) were male and the mean APACHE3 score was 81.1 ± 23.6 and 56.9 ± 22.7 in group 1 and group 2 respectively. Liver failure was noticed in 5 patients in group 1 and in 7 patients in group 2.

There was no statistically significant relationship between a patient's initial thiamine level and vitamin C level. Borrelli et al. followed SICU patients during their hospital course and found that those with low vitamin C levels were at higher risk of developing multi-organ failure. [24] Lamontagne et al [25] indicated that vitamin C monotherapy did

not reduce overall mortality. Therefore, the efficacy of vitamin C monotherapy in reducing overall mortality is uncertain and needs to include a large number of high-quality studies. Furthermore, low-quality studies indicated that vitamin C could improve the overall mortality of patients with sepsis, while high-quality studies did not show the same trend. Low-quality studies were mainly published in 2021. In the subgroup of years of publication, only the studies published in 2021 showed that vitamin C reduced overall mortality in patients with sepsis; the literature published in other time groups did not show the same trend. In the blind method subgroups, the unclear group showed an exciting result, but the scores of the included studies were less than or equal to 3. In other words, all the included studies were of low quality, indicating that low-quality literature can significantly affect the bias in outcomes. In the VICTOR trial [26], the baseline values of vitamin C were similar to what we reported in our study in the routine therapy and HAT groups, respectively, vs. 0.23 mg/dL in our study population. The authors comment that their baseline levels are significantly lower than those reported in the ORANGES, Marik et al., and CITRUS-ALI trials45. Finally, the ATESS trial investigators found that 50.9% of the HAT group and 47.3% of the placebo group were vitamin C deficient at the time of enrolment in the trial and that the median vitamin C level in the HAT group increased significantly over the first 72 h of therapy. [27] Thiamine deficiency in baseline samples was much less common, occurring in 9.4% of the HAT group and 7.0% of the placebo group. [27]

Conclusion

We found that mean ascorbic acid and thiamine levels were lower than normal range but that there was no relationship between these levels and outcomes, including 28 day mortality.

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