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Evaluation of the Effects of Vitamin C in Prognosis of Patients with Sepsis in Zanjan Vali- e-Asr Hospital in 2020

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ABSTRACT

Background & Objective: Regarding the high prevalence of sepsis, it is important to discover methods to control this condition. Valuable effect of vitamin C in vasopressin synthesis is demonstrated, moreover, its antioxidant effect reduces vascular infiltration. Therefore, the beneficial effects of vitamin C in prognosis of the patients who have been admitted to Vali-e- Asr hospital in Zanjan, Iran with the diagnosis of sepsis have been evaluated.

Materials & Methods: This cross sectional study was planned on patients with sepsis who have been admitted to the infectious ward of Vali-e-Asr hospital in Zanjan. Patients with sepsis above 18 years old from June to March 2020 have been included in this study. Data of patients whom have received intravenous vitamin C, 25 mg/kg/24h for 4 days, and patients without reception vitamin C was collected from their files. Their demographic, clinical and para clinical information were collected, then the information was analyzed.

Results: 54 patients (26 received vitamin C and 28 did not receive vitamin C) were enrolled in this study. Considering that the two groups were matched from the beginning of the study, no statistically significant difference was found between the two groups of patients in demographic characteristics. Furthermore, there were no significant differences in the sepsis induced complications, e.g. laboratory findings, mean days of hospitalization in ICU and SOFA score.

Conclusion: Our findings demonstrated that no clear statistically significant difference was found between the two groups of control and vitamin C received groups; nonetheless for precise conclusion more studies with larger groups are required.

Keywords: Sepsis, Vitamin C, Prognosis, Septic Shock, Sofa Score

Introduction

In the previous five decades sepsis is defined as a life-threatening organ dysfunction caused by a dysregulated host response to infection. The sepsis characterization was described by four systemic inflammatory response syndrome (SIRS) criteria consisting of tachycardia; tachypnea; fever or hypothermia; and leukocytosis, leukopenia or bandemia (1).

Severe sepsis was defined as sepsis complicated by organ dysfunction, which could progress to septic shock, defined as "sepsis-induced hypotension persisting despite adequate fluid resuscitation. The sepsis description expanded the list of diagnostic criteria, including a set of 24 general, inflammatory, hemodynamic, organ dysfunction or tissue perfusion parameters. In the sepsis-2 definition the criteria for severe sepsis stayed alike, whereas septic shock was defined more clearly as refractory hypotension even with sufficient fluid resuscitation (2). The 2016 Task Force also introduced the quick sequential organ failure assessment (SOFA), or qSOFA, score, composed of three components that are easy to measure at the bedside: respiratory rate of 22 breaths/min or greater, altered mentation and systolic blood pressure of 100 mm Hg or less. Evidence indicated that in out-of-hospital, emergency department and general hospital ward settings, adult patients with suspected infection and a higher risk for poor outcomes typical of sepsis can be rapidly identified by the presence of at least two qSOFA criteria. The rapid assessment tool such as SOFA was presented to grade sepsis severity and predicts in-hospital mortality based on well-defined multi-physiological criteria (3).

In the past 2 decades, numerous studies have suggested that the incidence of sepsis is increasing over time, while mortality is decreasing and sepsis is considered as a serious public health problem. The steady decrease of sepsis-related mortality over time most likely reflects the

overall improvement in ICU practice in the last 20 to 30 years. This is supported by the finding from the above-mentioned Australian and New Zealand ICU registry study which the observed annual reduction in mortality did not differ between patients with severe sepsis and other diagnoses. Key factors that contribute to the overall rise in the worldwide incidence of sepsis include the aging of the population, the emergence of antimicrobial resistance, the growing use of immunosuppressive drugs and therapies and the increased number of patients who are at risk for developing sepsis. In high-income countries, a global estimation of 31.5 million sepsis cases, with potentially 5.3 million annually deaths were reported (4). Due to the high prevalence of infectious disease such as malaria, HIV and dengue fever, sepsis is considered to be a substantial problem of out-hospital deaths in low-income countries (5, 6). Although mortality rate has diminished from 1990 to 2017 by 52.8% and the reported 11.0 million sepsis-related deaths annually still account for 19.7% of the total deaths (7).

Kim et al. showed that intravenous injection of vitamin C reduced lipid peroxidation and oxidative stress, which leads to the expression of the gene regulating liver vessels in polymicrobial sepsis, and in this way, the vitamin reduced liver micro vascular dysfunction in the course of sepsis in rats (8). Regarding endothelial dysfunction in SIRS, various clinical studies have been conducted on the beneficial effects of vitamin C in endothelial cells, especially in chronic stress conditions, which the results demonstrated improvement the function of endothelial cells in either insulin-dependent (9) or independent (10) diabetic patients with chronic hypertension (11). In these studies, vitamin C was administered intra-arterially or intravenously and the increased nitric oxide (NO) was suggested to the possibility of its protective effects against destruction by reactive oxygen species (ROS). The importance of the effect of NO on endothelial function is its role as a vasodilator and inhibition of platelet aggregation (12).

Lack of NO is pathological due to the effect on vascular endothelium and loss of micro vascular circulation (13, 14) on the other hand, high concentration of NO leads to increased vascular permeability in SIRS (15). Inducible nitric oxide synthase (iNOS) or neuronal nitric oxide synthase (nNOS) appear to facilitate sepsis-induced damage but endothelial nitric oxide synthase (eNOS) has protective effects in this case (16). It is important to know that iNOS expression leads to inflammation in almost all major cells of the body while eNOS is expressed by endothelial cells. Administration of vitamin C decreases iNOS (17, 18) but increases eNOS (19).

In addition to NO dysregulation, other endothelial cell changes such as endothelial cell apoptosis, up regulation of adhesion molecules, and pro-coagulant state (20) occur during SIRS and vitamin C seems to be effective in correcting these factors (19, 21-23). It has been found that in vitro vitamin C in human umbilical vein endothelial cells (HUVEC) in response to TNF-alpha reduces the expression of the endothelial cell adhesion molecule ICAM-1 (24) and leads to the suppression of neutrophil systemic discharge during sepsis, especially in the lung (25). Among the other beneficial effects of vitamin C in endothelial cells is the suppression of tissue factor production and regulation of response to inflammatory stimuli (26) and prevents excessive coagulation and vitamin C supplementation reduces the permeability and activation of fluids from the endothelium (27-29). The results of clinical studies have shown that different ways of administering vitamin C have different effects. So that the oral vitamin C supplement probably has relatively minor effects due to limited absorption and the maximum absorption of vitamin C is obtained with a dose of 200 mg (30). Higher doses cause diarrhea and abdominal cramps due to the effects of ascorbate accumulation in the intestinal lumen (31) which is why parenteral administration has been used in various studies. In a sample of studies, intravenous but not oral administration resulted in increased endothelial responsiveness (32).

In patients with both sepsis and septic shock, a combination therapy of hydrocortisone, vitamin C, and thiamine, compared with placebo, could diminish the duration of vasopressor use and SOFA scores during the first 72 h (33), moreover, it has been shown that destructive consequences of sepsis are reduced by vitamin C infusion in mice (34). It seems that vitamin C has a positive effect on the rate of organ failure and inflammatory responses and endothelial damage in patients with severe sepsis (35). Administration a diet containing vitamin C led to an improvement in the prognosis in the sepsis rat model by reducing inflammatory damage (36). The combined treatment of hydrocortisone, intravenous vitamin C and thiamine led to strengthening the immune system and organ damage and reduced the risk of death and organ failure following sepsis (37-41), however, in patients with septic shock, there was no change or slight improvement in the clinical relationship of health-related quality of life in people receiving combined treatment with vitamin C, corticosteroids and thiamine compared to placebo (42-46).

Because of the above mentioned discrepancies about vitamin C effects in sepsis, in the present study we evaluated the prognosis of the patients with sepsis who were admitted in Zanjan Vali-asr hospital with history of vitamin C administration in Feburary 2019 to June 2020.

Materials and Methods

This descriptive cross-sectional study was done in Vali-e-Asr hospital infectious disease department in sepsis patients older than 18 years from June to March 2020. The study was started after ethical committee approval (IR.ZUMS.REC.1399.082); moreover, questionnaires were filled and evaluation was anonymous.

Patients with diagnosis of sepsis who were admitted in Zanjan Vali-e-Asr Hospital from June to March 2020 enter the study. All of the patients were above 18 years old who were admitted with sepsis diagnosis. They were

divided into two groups. The first group was prescribed intra venous vitamin C and the second group did not receive vitamin C during hospitalization. These data were checked by files of patients whom admitted in the hospital during above mentioned period whom have been administered Vitamin C (25 mg/kg, IV, daily) for four days **(40, 47)**

At the beginning demographic data: gender, age, background disease, drug history (medicine) use, origin of sepsis and early complication of sepsis were evaluated.

In the present study both clinical complications (Loss of consciousness, septic shock and respiratory failure and some laboratory disturbances have been evaluated. Furthermore, mean days of hospitalization in ICU and Sofa score were evaluated too.

Statistical analysis

Qualitative data were analyzed by chi square and quantitative data were presented by mean±SD and analyzed by independent student's t test. P<0.05 was considered as significant.

Results

In the present experiment totally 54 patients; (26 patients which were received vitamin C, 25 mg/kg, IV, daily for four days) and (28 people without vitamin C reception) have been compared.

There were no statistical differences between demographic data in the beginning of evaluation: gender (p= 0.513), age (P= 0.569), background disease (P= 1), history of drugs (medicines) usage (P= 0.571), origin of sepsis (P= 1) and early complication of sepsis (P= 0.722) between the two groups (Table 1).

Table 1. Demographic data of patients in two groups were received vitamin C as test group (25 mg/kg, IV, daily for four days) and 28 people without vitamin C as control group. Vit. C: group which received vitamin C In the beginning of evaluation.

Variables	Units	Control	Vit. C	P.value
Gender: male	Number (percent)	17 (60.7)	18 (69.2)	0.513
Female		11 (39.3)	8 (30.8)	
Age	Year (Mean±SD)	62.07±17.69	59.42±16.14	0.569
Background Disease: Yes	Number (percent)	14 (50)	13 (50)	1
No		14 (50)	13 (50)	
History of drug (medicine) usage: Yes	Number (percent)	14 (50)	11 (42.3)	0.571
No		14 (50)	15 (57.7)	
Sepsis origin: Respiratory	Number (percent)	25 (89.3)	26 (100)	1
Urinary		1 (3.6)	0 (0)	
Soft tissues		1 (3.6)	0 (0)	
Arthrit		1 (3.6)	0 (0)	
Complications of sepsis: No	Number (percent)	15 (53.6)	17 (65.4)	0.722
Loss of consciousness		1 (3.6)	0 (0)	
Respiratory failure		1 (3.6)	0 (0)	
Others		11 (39.3)	9 (34.6)	

After four days of assessment, the evaluated clinical complications: Loss of consciousness (P= 1), septic shock (P= 0.596) and respiratory failure (P= 0.237) were not altered (Table 2).

Table 2. Clinical complications in two groups were received vitamin C as test group (25 mg/kg, IV, daily for four days) and 28 people without vitamin C as control group. Vit. C: group which received vitamin C for 4 days.

Variables		Units	Control	Vit. C	P.value
Loss of consciousness:	**No**	Number (percent)	27 (96.4)	25 (96.2)	1
	Yes		1 (3.6)	1 (3.8)	
Septic shock:	**No**	Number (percent)	26 (92.86)	26 (100)	0.596

Variables		Units	Control	Vit. C	P.value
	Yes		2 (7.14)	0 (0)	
Respiratory failure:	**Yes**	Number (percent)	3 (10.7)	0 (0)	0.237
	No		25 (89.3)	26 (100)	

After four days of evaluation, measured laboratory scales were not different: WBC (p=0.394), Hb (P=0.97), Platelet (P=0.524), BUN (P= 0.174), Cr (P= 0.149), BS (p=0.951), Na (P=0.184), K (P=0.371), ALT (P= 0.194), AST (P= 0.452), ALP (p=0.182), Ca (P=0.691), ESR (P=0.56), CRP (P= 0.591), Bilirubin-total (P= 0.719), Bilirubin-D (p=0.536), PT (P=0.562), INR (P=0.477), U/A (P= 0.612), U/C (P= 0.237) and B/C (P= 1) between two groups (Table 3).

Table 3. Some laboratory scales in two groups were received vitamin C as test group (25 mg/kg, IV, daily for four days) and 28 people without vitamin C as control group. Vit. C: group which received vitamin C for 4 days.

Variables	Units	Control	Vit. C	P.value
WBC	Number	10.33±4.08	9.34±4.41	0.394
Hb	Percent	13.55±1.93	13.53±2.55	0.97
Platlet	Number	228.64±82.81	242.19±71.49	0.524
BUN	mg/dL	21.21±8.62	18.22±7.25	0.174
Cr	mg/dL	1.21±0.41	1.08±0.18	0.149
FBS	mg/dL	125.14±80.87	123.96±55.83	0.951
Na	mEq/dL	138.75±4.71	137.04±4.6	0.184
K	mEq/dL	4.01±0.53	4.15±0.6	0.371
ALT	IU/L	41.68±29.57	54.69±42.43	0.194
AST	IU/L	46.46±33.16	53.85±38.31	0.452
ALP	IU/L	194.14±72.99	172.96±37.26	0.182
Ca	mEq/dL	8.57±0.98	8.67±0.88	0.691
ESR	mm/hr	21.85±9.98	20.31±9.38	0.56
CRP	mg/L	52.39±25.71	56.84±34.37	0.591
Bilirubin-total	mg/dL	1.05±0.52	1.00±0.31	0.719
Bilirubin-D	mg/dL	0.35±0.18	0.32±0.18	0.536
PT	second	14.21±1.24	14.02±1.16	0.562
INR	Ratio	1.13±0.14	1.1±0.14	0.477
U/A Negative	Number (Percent)	25 (89.3)	25 (96.2)	0.612
Positive		3 (10.7)	1 (3.8)	
U/C Negative	Number (Percent)	25 (89.3)	26 (100)	0.237
Positive		3 (10.7)	0 (0)	
B/C Negative	Number (Percent)	28 (100)	26 (100)	1
Positive		0 (0)	0 (0)	

Either mean days hospitalization in ICU (p= 0.919) or Sofa score (P= 0.711) were not changed after four days of evaluation (Table 4).

Table 4. Mean days hospitalization in ICU, Sofa, scores in two groups were received vitamin C as test group (25 mg/kg, IV, daily for four days) and 28 people without vit. C as control group and vitamin C: group which received vitamin C after 4 days.

Variables	Units	Control	Vit. C	P.value
Mean days hospitalization in ICU	days	10.54±3.24	10.62±2.4	0.919
Sofa score	Number±SD	2.25±0.58	2.31±0.55	0.711

Discussion

Sepsis was defined as (documented or suspected) infection leading to the onset of SIRS as reflected by the presence of two or more SIRS criteria. Septic shock is defined as a subcategory of sepsis patients followed by circulatory and cellular/metabolic dysfunction (3). There is information which has been showed no change or modest improvement and questionable in clinical relevance in the health-related quality of life in patients with septic shock treated with vitamin C alone or in combination compared to placebo (42-46).

In the beginning the demographic data [gender, age, background disease, history of drugs (medicines) use, origin of sepsis and early complication of sepsis] were evaluated. They were not statistically different which indicated that two groups have been matched.

There were no statistical differences between some laboratory scales (WBC, Hb, Platelet, BUN, Cr, BS, Na, K, ALT, AST, ALP, Ca, ESR, CRP, Bilirubin-total, Bilirubin-D, PT, INR, U/A, U/C and B/C) after four days of evaluation between test and control groups. Iglesias et al. has shown these results too moreover the same results have been illustrated by Litwak and his colleagues (40 and 47).

Our data indicated that the mean days hospitalization in ICU was not different in two groups. A meta-analysis from 10 studies (4 randomized controlled trials [RCTs] and 6 retrospective studies) which involving 1671 patients (495 in the vitamin C treatment group and 1176 in the control group) disclosed that the use of vitamin C did not reduce the length of ICU or hospital stay (48). Moreover, Zabet et al., indicated that vitamin C administration showed no effect on hospital duration stay (49), Mitchell et al., study revealed that the hospital length of stay did not changed by vitamin C administration after 12 and 24-month follow-up (50). Fowler et al. indicated this result by a randomized, double-blind, placebo-controlled, multicenter trial which conducted in seven medical intensive care units in the United States, enrolling patients (N = 167) with sepsis (51).

At last Sofa score was assessed which no statistical differences between two groups have been seen after four days of evaluation. The same results have been demonstrated by other investigations. Iglesias et al. demonstrated no significant differences in SOFA score in a combination therapy of IV vitamin C, thiamine and hydrocortisone in 137 patients were randomized to the treatment (n = 68) and control group (n = 69) (48). Fowler et al. showed reduced sofa score in twenty four randomized patients with severe sepsis in intensive care unit whom received intravenous infusions every six hours for four days of vitamin C (35).

Moreover, a randomized trial in 205 patients (103 with intervention and 102 with placebo group) treated with combination parenteral vitamin C (1500 mg), hydrocortisone (50 mg) plus thiamine (100 mg) every 6 hours for 4 days versus placebo in matching volumes at the same time points did not reduced sofa csore (52). Weilan et al. proved by nine RCTs, enrolling 1427 patients of sepsis and septic shock treated with vitamin C, hydrocortisone plus thiamine (717) or only standard care (710) that this combination therapy slightly improved the SOFA score in the first 72 h in patients with sepsis (53).

Rosengrave et al. did not found a significant decreases in the sofa score by a double-blind, randomized placebo-controlled trial in 40 patients with septic shock who receive intravenous vitamin C (at a dose of 25 mg/kg every 6 h) or placebo (intravenous 5% dextrose) (54).

A systematic review and meta-analysis of 20 randomized clinical trials (2124 participants) showed that vitamin C alone or combined with thiamine and/or hydrocortisone, compared to placebo, standard care or hydrocortisone showed a little to no difference or very uncertain evidence for SOFA score improvement (53) but a meta-analysis conducted by Wu et al. which consists six randomized controlled trials (RCTs) and seven observational studies enrolling 1,559 patients were included (762 were treated with combination therapy of hydrocortisone, vitamin C, and thiamine, and 797 were treated with hydrocortisone alone, standard care or placebo) in patients with sepsis and septic shock, showed a reduction in the SOFA scores during the first 72 h (33).

Conclusion

Our finding demonstrated that there were no significant differences between control and vitamin C received groups nonetheless for precise conclusions more studies with a larger groups are required.

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None.

Conflict of Interest

The authors declare no conflict of interest.

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None Declared.

References

1. Zhang YY, Ning BT. Signaling pathways and intervention therapies in sepsis. Signal Transduct Target Ther. 2021;6(1):407. [PMID] [PMCID] [DOI:10.1038/s41392-021-00816-9]
2. Singer M, Deutschman CS, Seymour CW, et al. The third international consensus definitions for sepsis and septic shock (Sepsis-3). JAMA. 2016; 315(8):801-10. [DOI:10.1001/jama.2016.0287] [PMID] [PMCID]
3. Goldstein B, Giroir B, Randolph A. International consensus conference on pediatrics. International pediatric sepsis consensus conference: definitions for sepsis and organ dysfunction in pediatrics. Pediatr Crit Care Med. 2005;6(1):2-8.[PMID] [DOI:10.1097/01.PCC.0000149131.72248.E6]
4. Fleischmann C, Scherag A, Adhikari NK, et al. Assessment of global incidence and mortality of hospital-treated sepsis. Current estimates and limitations. Am J Respir Crit Care Med. 2016; 193(3):259-72. [PMID] [DOI:10.1164/rccm.201504-0781OC]
5. Becker JU, Theodosis C, Jacob ST, Wira CR, Groce NE. Surviving sepsis in low-income and middle-income countries: new directions for care and research. Lancet Infect Dis. 2009;9(9):577-82. [DOI:10.1016/S1473-3099(09)70135-5] [PMID]
6. van den Boogaard W, Manzi M, Harries AD, Reid AJ. Causes of pediatric mortality and case-fatality rates in eight Medecins Sans Frontieres-supported hospitals in Africa. Public Health Action. 2012; 2(4):117-21. [DOI:10.5588/pha.12.0038] [PMID] [PMCID]
7. Rudd KE, Johnson SC, Agesa KM, et al. Global, regional, and national sepsis incidence and mortality, 1990-2017: analysis for the Global Burden of Disease Study. Lancet. 2020; 395(10219):200-11. [PMID] [DOI:10.1016/S0140-6736(19)32989-7]
8. Kim JY, Lee SM. Effect of ascorbic acid on hepatic vasoregulatory gene expression during polymicrobial sepsis. Life Sci. 2004;75(16):2015-26. [DOI:10.1016/j.lfs.2004.06.002] [PMID]
9. Timimi FK, Ting HH, Haley EA, Roddy MA, Ganz P, Creager MA. Vitamin C improves endothelium-dependent vasodilation in patients with insulin-dependent diabetes mellitus. J Am Coll Cardiol. 1998;31(3):552-7. [DOI:10.1016/S0735-1097(97)00536-6]
10. Ting HH, Timimi FK, Boles KS, Creager SJ, Ganz P, Creager MA. Vitamin C improves endothelium-dependent vasodilation in patients with non-insulin-dependent diabetes mellitus. J Clin Invest. 1996;97(1):22-8. [DOI:10.1172/JCI118394] [PMID] [PMCID]
11. Solzbach U, Hornig B, Jeserich M, Just H. Vitamin C improves endothelial dysfunction of epicardial coronary arteries in hypertensive patients. Circulation. 1997;96(5):1513-9. [DOI:10.1161/01.CIR.96.5.1513] [PMID]
12. Jackson WF. The endothelium-derived relaxing factor. J Reconstr Microsurg. 1989;5(3):263-71. [DOI:10.1055/s-2007-1006876] [PMID]
13. Tyml K, Li F, Wilson JX. Septic impairment of capillary blood flow requires nicotinamide adenine dinucleotide phosphate oxidase but not nitric oxide synthase and is rapidly reversed by ascorbate through an endothelial nitric oxide synthase-dependent mechanism. Crit Care Med. 2008;36(8):2355-62. [PMID] [PMCID] [DOI:10.1097/CCM.0b013e31818024f6]
14. Naseem KM. The role of nitric oxide in cardiovascular diseases. Mol Aspects Med. 2005; 26(1-2):33-65. [DOI:10.1016/j.mam.2004.09.003] [PMID]
15. De Cruz SJ, Kenyon NJ, Sandrock CE. Bench-to-bedside review: the role of nitric oxide in sepsis. Expert Rev Respir Med. 2021;(5)3:9. [DOI:10.1586/ers.09.39] [PMID]
16. Parratt JR. Nitric oxide in sepsis and endotoxaemia. J Antimicrob Chemother. 1998;41 Suppl A:31-9. [DOI:10.1093/jac/41.suppl_1.31] [PMID]
17. Wu F, Tyml K, Wilson JX. Ascorbate inhibits iNOS expression in endotoxin- and IFN gamma-stimulated rat skeletal muscle endothelial cells. FEBS Lett. 2002;520(1-3):122-6. [DOI:10.1016/S0014-5793(02)02804-1] [PMID]
18. Wu F, Wilson JX, Tyml K. Ascorbate inhibits iNOS expression and preserves vasoconstrictor responsiveness in skeletal muscle of septic mice. Am J Physiol Regul Integr Comp Physiol. 2003; 285(1):R50-6. [DOI:10.1152/ajpregu.00564.2002] [PMID]
19. Ulker S, McKeown PP, Bayraktutan U. Vitamins reverse endothelial dysfunction through regulation of eNOS and NAD(P)H oxidase activities. Hypertension. 2003;41(3):534-9. [PMID] [DOI:10.1161/01.HYP.0000057421.28533.37]
20. Keel M, Trentz O. Pathophysiology of polytrauma. Injury. 2005;36(6):691-709. [DOI:10.1016/j.injury.2004.12.037] [PMID]

21. Rossig L, Hoffmann J, Hugel B, et al. Vitamin C inhibits endothelial cell apoptosis in congestive heart failure. Circulation. 2001;104(18):2182-7. [DOI:10.1161/hc4301.098284] [PMID]

22. Saeed RW, Peng T, Metz CN. Ascorbic acid blocks the growth inhibitory effect of tumor necrosis factor-alpha on endothelial cells. Exp Biol Med (Maywood). 2003;228(7):855-65. [DOI:10.1177/15353702-0322807-12] [PMID]

23. Fiorito C, Rienzo M, Crimi E, et al. Antioxidants increase number of progenitor endothelial cells through multiple gene expression pathways. Free Radic Res. 2008;42(8):754-62. [DOI:10.1080/10715760802357057] [PMID]

24. Mo SJ, Son EW, Rhee DK, Pyo S. Modulation of TNF-alpha-induced ICAM-1 expression, NO and H2O2 production by alginate, allicin and ascorbic acid in human endothelial cells. Arch Pharm Res.2003;26(3):244-51. [DOI:10.1007/BF02976837] [PMID]

25. Martin WJ. Neutrophils kill pulmonary endothelial cells by a hydrogen-peroxide-dependent pathway. An in vitro model of neutrophil-mediated lung injury. Am Rev Respir Dis. 1984;130(2):209-13. [DOI:10.1164/arrd.1984.130.2.209] [PMID]

26. Chen YH, Lin SJ, Chen YL, Liu PL, Chen JW. Anti-inflammatory effects of different drugs/agents with antioxidant property on endothelial expression of adhesion molecules. Cardiovasc Hematol Disord Drug Targets. 2006; 6(4):279-304. [DOI:10.2174/187152906779010737] [PMID]

27. May JM, Qu ZC. Ascorbic acid prevents increased endothelial permeability caused by oxidized low density lipoprotein. Free Radic Res. 2010;44(11): 1359-68. [DOI:10.3109/10715762.2010.508496] [PMID] [PMCID]

28. Wilson JX. Mechanism of action of vitamin C in sepsis: ascorbate modulates redox signaling in endothelium. Biofactors. 2009;35(1):5-13. [DOI:10.1002/biof.7] [PMID] [PMCID]

29. Utoguchi N, Ikeda K, Saeki K, et al. Ascorbic acid stimulates barrier function of cultured endothelial cell monolayer. J Cell Physiol. 1995;163(2):393-9. [DOI:10.1002/jcp.1041630219] [PMID]

30. Levine M, Conry-Cantilena C, Wang Y, et al. Vitamin C pharmacokinetics in healthy volunteers: evidence for a recommended dietary allowance. Proc Natl Acad Sci U S A. 1996;93(8): 3704-9. [DOI:10.1073/pnas.93.8.3704] [PMID] [PMCID]

31. Hathcock JN, Azzi A, Blumberg J, et al. Vitamins E and C are safe across a broad range of intakes. Am J Clin Nutr. 2005;81(4):736-45. [DOI:10.1093/ajcn/81.4.736] [PMID]

32. Ichim TE, Minev B, Braciak T, et al. Intravenous ascorbic acid to prevent and treat cancer-associated sepsis? J Transl Med. 2011;9:25. [DOI:10.1186/1479-5876-9-25] [PMID][PMCID]

33. Wu T, Hu C, Huang W, Xu Q, Hu B, Li J. Effect of combined hydrocortisone, ascorbic acid and thiamine for patients with sepsis and septic shock: A systematic review and meta-analysis. Shock. 2021;56(6):880-9. [DOI:10.1097/SHK.0000000000001781] [PMID]

34. Fisher BJ, Kraskauskas D, Martin EJ, et al. Mechanisms of attenuation of abdominal sepsis induced acute lung injury by ascorbic acid. Am J Physiol Lung Cell Mol Physiol. 2012;303(1):L20-32. [DOI:10.1152/ajplung.00300.2011] [PMID]

35. Fowler AA, Syed AA, Knowlson S, et al. Phase I safety trial of intravenous ascorbic acid in patients with severe sepsis. J Transl Med. 2014;12:32. [DOI:10.1186/1479-5876-12-32] [PMID] [PMCID]

36. Kawade N, Tokuda Y, Tsujino S, et al. Dietary intake of ascorbic acid attenuates lipopolysaccharide-induced sepsis and septic inflammation in ODS rats. J Nutr Sci Vitaminol (Tokyo). 2018;64(6):404-11. [DOI:10.3177/jnsv.64.404] [PMID]

37. Marik PE. Patterns of death in patients with sepsis and the use of hydrocortisone, ascorbic acid, and thiamine to prevent these deaths. Surg Infect (Larchmt). 2018;19(8):812-20. [DOI:10.1089/sur.2018.111] [PMID]

38. Moskowitz A, Andersen LW, Huang DT, et al. Ascorbic acid, corticosteroids, and thiamine in sepsis: a review of the biologic rationale and the present state of clinical evaluation. Crit Care. 2018;22(1):283. [PMID] [PMCID] [DOI:10.1186/s13054-018-2217-4]

39. Moskowitz A, Yankama T, Andersen LW, et al. Ascorbic acid, corticosteroids and thiamine in sepsis (ACTS) protocol and statistical analysis plan: a prospective, multicentre, double-blind, randomised, placebo-controlled clinical trial. BMJ Open. 2019;9(12):e034406. [PMID] [PMCID] [DOI:10.1136/bmjopen-2019-034406]

40. Iglesias J, Vassallo AV, Patel VV, Sullivan JB, Cavanaugh J, Elbaga Y. Outcomes of Metabolic Resuscitation Using Ascorbic Acid, Thiamine, and Glucocorticoids in the early treatment of sepsis: The organes trial. Chest. 2020;158(1):164-73. [DOI:10.1016/j.chest.2020.02.049] [PMID]

41. Kim J, Arnaout L, Remick D. Hydrocortisone, ascorbic acid, and thiamine (HAT) therapy decreases oxidative stress, improves cardiovascular function, and improves survival in murine sepsis. Shock. 2020;53(4):460-7. [DOI:10.1097/SHK.0000000000001385] [PMID]

42. Grossestreuer AV, Moskowitz A, Andersen LW, et al. Effect of ascorbic acid, corticosteroids, and thiamine on health-related quality of life in sepsis. Crit Care Explor. 2020;2(12):e0270. [PMCID] [DOI:10.1097/CCE.0000000000000270] [PMID]

43. Marik PE, Varon J, Surani SR. Hydrocortisone, ascorbic acid and thiamine for sepsis: Is the jury out? World J Diabetes. 2020;11(4):90-4. [DOI:10.4239/wjd.v11.i4.90] [PMID] [PMCID]

44. Assouline B, Faivre A, Verissimo T, et al. Thiamine, ascorbic acid, and hydrocortisone as a metabolic resuscitation cocktail in sepsis: A meta-analysis of randomized controlled trials with trial sequential analysis. Crit Care Med. 2021;49(12): 2112-20. [PMID] [DOI:10.1097/CCM.0000000000005262]

45. Fong KM, Au SY, Ng GWY. Steroid, ascorbic acid, and thiamine in adults with sepsis and septic shock: a systematic review and component network meta-analysis. Sci Rep. 2021;11(1): 15777. [DOI:10.1038/s41598-021-95386-9] [PMID] [PMCID]

46. Lee YR, Vo K, Varughese JT. Benefits of combination therapy of hydrocortisone, ascorbic acid and thiamine in sepsis and septic shock: A systematic review. Nutr Health. 2022;28(1):77-93. [DOI:10.1177/02601060211018371] [PMID]

47. Litwak JJ, Cho N, Nguyen HB, Moussavi K, Bushell T. Vitamin C, hydrocortisone, and thiamine for the treatment of severe sepsis and septic shock: A retrospective analysis of real-world application. J Clin Med. 2019;8(4). [DOI:10.3390/jcm8040478] [PMID] [PMCID]

48. Iglesias J, Vassallo AV, Liesenfeld O, et al. A 33-mRNA classifier is able to produce inflammopathic, adaptive, and coagulopathic endotypes with prognostic significance: The outcomes of metabolic resuscitation using ascorbic acid, thiamine, and glucocorticoids in the early treatment of sepsis (ORANGES) trial. J Pers Med. 2021;11(1):9. [DOI:10.3390/jpm11010009] [PMID] [PMCID]

49. Zabet MH, Mohammadi M, Ramezani M, Khalili H. Effect of high-dose ascorbic acid on vasopressor's requirement in septic shock. J Res Pharm Pract. 2016; 5(2):94-100. [PMID] [PMCID] [DOI:10.4103/2279-042X.179569]

50. Mitchell AB, Ryan TE, Gillion AR, Wells LD, Muthiah MP. Vitamin C and thiamine for sepsis and septic shock. Am J Med. 2020;133(5):635-638. [DOI:10.1016/j.amjmed.2019.07.054] [PMID]

51. Fowler AA, Truwit JD, Hite RD, et al. Effect of vitamin C infusion on organ failure and biomarkers of inflammation and vascular injury in patients with sepsis and severe acute respiratory failure: The CITRIS-ALI randomized clinical trial. JAMA. 2019; 322(13):1261-1270. [PMID] [DOI:10.1001/jama.2019.11825] [PMCID]

52. Moskowitz A, Huang DT, Hou PC, et al.Effect of ascorbic acid, corticosteroids, and thiamine on organ injury in septic shock: The ACTS randomized clinical trial. JAMA. 2020;324(7): 642-650. [DOI:10.1001/jama.2020.11946] [PMID] [PMCID]

53. Na W, Shen H, Li Y, Qu D. Hydrocortisone, ascorbic acid, and thiamine (HAT) for sepsis and septic shock: a meta-analysis with sequential trial analysis. J Intensive Care 2021; 9(1):75. [PMID] [DOI:10.1186/s40560-021-00589-x] [PMCID]

54. Rosengrave P, Spencer E, Williman J, et al. Intravenous vitamin C administration to patients with septic shock: a pilot randomised controlled trial. Crit Care. 2022; 26(1):26. [PMID] [PMCID] [DOI:10.1186/s13054-022-03900-w]

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