Immunopathologia Persa
DOI:10.34172/ipp.2022.08
http www.immunopathol.com

The effect of vitamin E and vitamin C in patients with COVID-19 pneumonia; a randomized controlled clinical trial

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Received 20 Dec. 2020
Accepted 19 Feb. 2021
Published online 14 Apr. 2021

Keywords: COVID-19, Vitamin C, Vitamin E, Clinical trial

Abstract

Introduction: Cytokine storm and oxidative stress play a key role in the pathogenesis of coronavirus disease 2019 (COVID-19). Vitamins C and E are two known antioxidants with possible theoretical beneficial effects in COVID-19 patients.
Objectives: This study aimed to clinically evaluate the effects of the combination of these agents as adjunctive therapy with the standard treatment in the outcome of COVID-19 patients.
Patients and Methods: Hospitalized non-severe COVID-19 patients were randomly divided into two groups of intervention (n=38) and control (n=34) to receive either oral vitamin C 1000 mg daily plus oral vitamin E 400 IU daily in addition to the national standard treatment regimen (hydroxychloroquine) or standard regimen alone, respectively, during the hospitalization period until hospital discharge or ICU admission. The clinical response of patients at the end of treatment (either cure, improvement, or failure), the duration of hospitalization, and the mortality rate were recorded and compared between the groups.
Results: During the study, three patients in the intervention group (7.89%) and five patients in the control group (14.71%) had treatment failure, while all other patients had clinical improvement (P = 0.380). The duration of hospitalization was shorter in the intervention group (7.95 ± 3.18 days) compared to the control group (8.03 ± 2.83 days); however, the difference was not statistically significant (P = 0.821). Furthermore, no patients in both groups died during the study.
Conclusion: The combination of oral vitamins C (1000 mg daily) and E (400 IU daily) has no beneficial effect in COVID-19 patients.
Trial Registration: Registration of trial protocol has been approved in Iranian registry of clinical trials (identifier: IRCT20180425039414N3; https://www.irct.ir/trial/48083, ethical# IR.MUI.MED.REC.1399.047).

Citation: Hakamifard A, Soltani R, Maghsoudi A, Rismanbaf A, Aalinezhad M, Tarrahi MJ, Mashayekhbakhsh S, Dolatshahi K. The effect of vitamin E and vitamin C in patients with COVID-19 pneumonia; a randomized controlled clinical trial. Immunopathol Persa. 2022;8(1):e08. DOI:10.34172/ipp.2022.08.

Introduction

Coronavirus disease 2019 (COVID-19) is a newly developed human disease caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). The outbreak was first reported in December 2019 in Wuhan, China and it was recognized as a pandemic disease by the World Health Organization (WHO) on March 11, 2020 due to the unusually high contagion rate of the virus (1). Due to the novelty of SARS-CoV-2 and lack of sufficient information about its pathogenicity, there is no vaccine for COVID-19, and there are doubts about treatments.

The most common clinical manifestations of COVID-19 are fever, fatigue, dry cough, anorexia, myalgia, and dyspnea, and mostly involving the lung tissue (2). However, COVID-19 is a multi-organ disease that can cause cardiovascular, liver, kidney, gastrointestinal, and neurological complications in addition to respiratory

Key point

In a randomized controlled clinical trial on two groups of intervention (n=38) and control (n=34) to receive either oral vitamin C 1000 mg daily plus oral vitamin E 400 IU daily in addition to the national standard treatment regimen (hydroxychloroquine) or standard regimen alone, we found the combination of oral vitamins C (1000 mg daily) and E (400 IU daily) has no beneficial effect in COVID-19 patients.

complications (3-5). The most important known mechanisms of the SARS-CoV-2 are cytokine storm (release of large amounts of pro-inflammatory cytokines and chemokines), increased inflammation and oxidative stress that cause serious side effects ARDS (including acute respiratory distress syndrome), acute lung injury (ALI), and organ damage (6). Disruption of the thiol redox circuits and macromolecule damage by oxidative stress can result in cell injury, and finally organ damage in COVID-19 patients (7).

Vitamin C (ascorbic acid) is a water-soluble vitamin that can protect proteins, lipids, and DNA from oxidation due to its antioxidant effects. This vitamin can also support the epithelial barrier against pathogens and help with innate and adaptive immunity (8). Vitamin C deficiency can increase the risk of infections. According to the reports, serum levels of vitamin C are significantly lower in patients with septic shock compared with the patients with non-septic shock, and the incidence of organ damage is inversely related to the level of vitamin C (8,9).

Vitamin E (alpha-tocopherol) is also one of the most well-known fat-soluble antioxidants that trap peroxyl radicals and breaks the chain reaction of lipid peroxidation in cell membranes and lipoproteins (10). This vitamin can also be effective in the development and function of dendritic cells, macrophages, natural killer (NK) cells, B cells, and T cells (11). It has been reported that serum levels of vitamin E are lower in critically ill patients with acute respiratory distress syndrome (ARDS), as one of the most important side effects of COVID-19 (12).

Objectives

This study aimed to evaluate the effects of the combination of vitamins C and E as adjunctive therapy with the standard treatment in the outcome of COVID-19 patients.

Patients and Methods

Study design

This was a randomized controlled clinical trial conducted in Amin hospital of Isfahan, Iran, affiliated to Isfahan University of Medical Sciences, from March to April 2020.

Patient selection

The study population selected from the patients referred to Amin hospital with the following inclusion criteria; (1) Age of 18 or more, (2) the diagnosis of COVID-19 based on the positive reverse transcription-polymerase chain reaction (RT-PCR) test for SARS-CoV-2 and chest computerized tomography (CT) scan by an infectious diseases specialist, and (3) hospitalization.

Patients with the following conditions were excluded from the study; (1) intubation (mechanical ventilation), (2) O_2 saturation below 85%, (3) respiratory rate (RR) more than or equal to 30, (3) allergic reaction to the study drugs, (4) shortness of breath due to cardiogenic pulmonary edema, (5) pregnancy, (6) lactation, (7) current hypoxia and oxygen therapy at home, (8) end-stage lung disease, (9) malignancy, (10) *glucose-6-phosphate dehydrogenase deficiency* (G6PD) deficiency, (11) diabetic ketoacidosis, (12) symptomatic kidney stones, (13) coagulation disorders, (14) under treatment with anticoagulants, (15) cardiac arrhythmias, and (16) immunodeficiency.

Interventions

Patients with inclusion criteria were randomly divided into two groups of intervention and control. Randomization was conducted using an online random number generator available at https://www.random.org/sequences, thereby even and odd numbers were considered for intervention and control groups, respectively. Demographic information and clinical findings including age, gender, initial diagnosis, underlying disease, WBC (white blood cell) count, ESR (erythrocyte sedimentation rate), and CRP (C-reactive protein) and lactate dehydrogenase (LDH) serum levels were recorded for all patients before any intervention. Patients in the control group received hydroxychloroquine (Amin Co., Iran) 400 mg on the first day followed by 200 mg every 12 hours as the national standard treatment and patients in the intervention group received oral vitamin C (OSVE Co., Iran) 1 g daily and oral vitamin E (Daana Co., Iran) 400 IU daily in addition to the mentioned standard treatment regimen. The mentioned drugs were administered for the duration of hospitalization in both groups until hospital discharge or intensive care unit (ICU) admission. In addition, supportive measures including nasal oxygen, hemodynamic control, glycemic control, fever control, and antibacterial agent administration (for suspected bacterial pneumonia) were done as necessary. During the study, clinical status (including cessation of fever, improvement of shortness of breath, and reduction of cough), oxygen saturation (SaO2), and hemodynamic parameters were monitored daily.

Outcome measures

The primary outcome measure was the clinical response of the patients at the end of treatment in three ways; cure (complete elimination of clinical symptoms), improvement (elimination of some primary clinical symptoms), and failure (continued or exacerbated primary symptoms). The judgment in this regard was made by an infectious diseases specialist and an internist physician.

The secondary outcome measures were the duration of hospitalization until hospital discharge or death, mortality rate during the study, and the mean of laboratory variables. The criteria for the hospital discharge, according to the national guidelines, were; (1) cessation of fever for 48-72 hours after discontinuation of the antipyretic drug, (2) significant improvement in chest X-ray, (3) the partial pressure of oxygen (PO_2) more than 93% without a ventilator at ambient air, and (4) improvement of clinical signs and symptoms including respiratory status and vital signs at the discretion of the treating physician.

Statistical analysis

Statistical analysis of data was performed with SPSS software version 24. The chi-square test was used to compare the clinical response and the mortality rates, while, due to non-normality of data distribution, the Mann-Whitney U test was used to compare the quantitative variables including the duration of hospitalization and laboratory parameters between the groups. $P < 0.05$ was considered statistically significant.

Results

Over the study period, 96 patients were evaluated for eligibility that 73 of whom met the inclusion criteria and were randomized. One patient in the intervention group was excluded from the trial due to pulmonary thromboembolism (PTE) and the need for anticoagulant therapy. Finally, 38 and 34 patients in the intervention and control groups, respectively, completed the study (Figure 1). Table 1 shows patients' baseline demographic, clinical, and laboratory data. As shown, both groups were matched regarding these characteristics.

During the study, three patients in the intervention group (7.89%) and 5 patients in the control group (14.71%) had treatment failure necessitating ICU admission, while all other patients, including 35 patients in the intervention group and 29 patients in the control group, had clinical improvement. No patients had clinical cure ($P = 0.380$).

The duration of hospitalization was shorter in the intervention group (7.95 ± 3.18 days) compared to the control group (8.03 ± 2.83 days); however, the difference was not statistically significant ($P = 0.821$). Furthermore, no patients in both groups died during the study.

Table 2 shows the comparison of vital signs and laboratory parameters between the groups in the evaluated time points (days 4, 6, and 8 of the study as well as the time of discharge). As shown, RR was significantly lower in the intervention group compared to the control group at days 4 and 8. Additionally, although the percentages of neutrophils and lymphocytes were significantly different between the groups at days 4 and 8 and time of discharge, all values were at normal range (55%-70% for neutrophils and 20%-40% for lymphocytes).

Discussion

Our study showed that supplementation of COVID-19 patients with oral vitamins C and E has no significant effect on the clinical outcome.

The importance of this study lies in observing the clinical effect of combination of two antioxidant treatment as a safe and economic intervention in treatment of COVID-19, which has been limited studied before.

COVID-19 is a systemic and multi-organ disease that can lead to cytokine storm and subsequent lung capillary endothelial cell activation, infiltration of neutrophils, and increased oxidative stress (13).

Oxidative stress results in severe hypoxemia, inflammation, and damage to the alveolar-capillary barrier, leading to acute respiratory distress syndrome (ARDS) and acute lung injury (ALI), both of which are the most important reasons for the admission of COVID-19 patients to the intensive care unit (ICU) (13,14). Additionally, interleukin-6 (IL-6) and endothelin-1

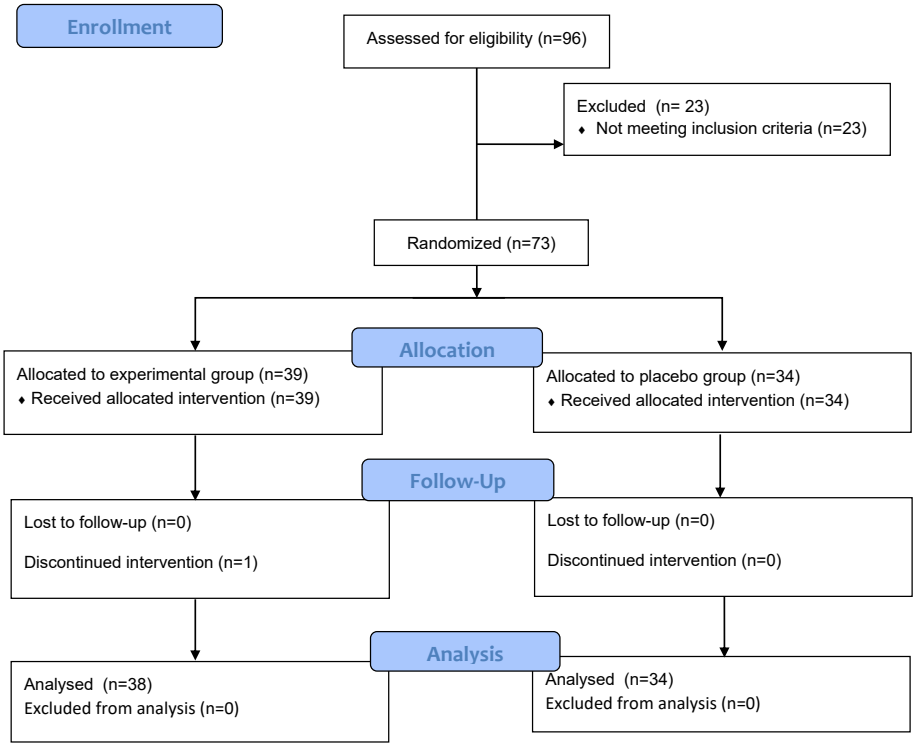

Figure 1. CONSORT Flow Diagram of the study.

Table 1. Baseline demographic, clinical, and laboratory characteristics of study patients

Variable	Group		*P* value
	Intervention (n = 38)	Control (n = 34)	
Age (years; mean ± SD)	35.68	37.41	0.726
Gender, (n & % of male)	24 (63.2%)	22 (64.7%)	0.810
Smoking (n)	3	2	0.553
Comorbidity (n)			
Diabetes	10	8	0.501
Hypertension	11	7	0.294
Hyperlipidemia	3	3	0.608
Cardiovascular disease	4	3	0.563
Vital signs (mean ± SD)			
T (°C)	37.13 ± 0.66	37.28 ± 0.71	0.166
PR (beats/min)	93.21 ± 14.15	94.44 ± 13.62	0.830
RR (breaths/min)	19.79 ± 2.55	20.59 ± 3.24	0.324
Laboratory data (mean ± SD)			
WBC (cells/mm^3)	6250.00 ± 2477.55	6476.47 ± 2649.88	0.787
Neut. (% of WBC)	68.85 ± 13.97	69.00 ± 11.65	0.978
Lymph. (% of WBC)	23.15 ± 12.48	24.84 ± 9.81	0.310
Plt (cells/mm^3)	207526.32 ± 76924.23	209411.76 ± 68341.88	0.640
O2 Sat. (%)	90.29 ± 15.35	89.52 ± 16.03	0.414
ESR (mm/h)	31.53 ± 21.96	31.32 ± 21.04	0.888
LDH (U/L)	550.18 ± 191.72	658.38 ± 433.67	0.284

(ET-1) seem to play a crucial role in the development of inflammation and oxidative stress in COVID-19 patients (15). IL-6 is a multifunctional inflammatory cytokine that has been shown to play role in cytokine storm in previous strains of the coronavirus, since ET-1 is a vasoconstrictor and inflammatory cytokine involved in pneumonia, pulmonary hypertension, interstitial lung fibrosis, and ARDS (15).

Neutrophil-related cytokine storm in covid-19 was reported to be associated with the severity and death of patients. Th17, an IL-17 secreting CD4+ T cell, has a unique link to augment the function of neutrophils (16).

Vitamin D3 supplementation via vitamin D receptor (VDR) led to an increase in anti-inflammatory and immunoregulating interleukin 10 (IL-10) cytokines and reduced frequency in Th17 cells, hence it could efficiently suppress the cytokine production of Th17 (17-19).

Vitamin C could decrease the number of neutrophils, escort the apoptotic process, and avoid inflammatory necrosis following the activation of neutrophil (16).

It was shown that compounds that reduce the secretion of inflammatory cytokines during the cytokine storm can be considered as the candidates for the treatment of COVID-19.

Vitamins C and E are water-soluble and fat-soluble vitamins, respectively, which are known to be potent antioxidants. According to studies, vitamin C can improve the function of the immune system and prevent the increase of inflammatory cytokines in the cytokine storm syndrome. Besides, vitamin C has antioxidant effects and able to reduce oxidative stress and inflammation in COVID-19 patients (15,20). Vitamin C can also reduce the secretion of IL-6 from endothelium induced by ET-1 (15). Other effects of vitamin C include preventing pneumonia, shortening the period of mechanical ventilation, and the ICU stay (13,20,21). Vitamin C has also been reported to have mild antihistamine effects that can help to improve the flulike symptoms such as sneezing, swollen sinuses, and runny nose, which can also be seen in COVID-19 patients (22).

In a case series conducted by Hiedra et al, it was detected that the administration of one gram of intravenous vitamin C every 8 hours for three days reduced inflammatory markers of ferritin and D-dimer. In addition, the FiO2 requirement showed a trend toward reduction but did not reach statistical significance (23).

Vitamin E deficiency has also been reported to cause impaired immune function and increase the pathogenicity of viral infections (22). In addition, animal studies have shown that vitamin E has beneficial impact on the immune system and reduces inflammation and viral load (22).

In a recent meta-analysis of 135 967 individuals in 19 clinical trials, analysis show high-dosage (≥400 IU/d) vitamin E supplements may increase all-cause mortality and should be avoided. A dose-response analysis showed a statistically significant relationship between vitamin E dosage and all-cause mortality, with increased risk of dosages greater than 150 IU/d. Although the generalizability of the findings to healthy adults is uncertain (24).

Despite the beneficial effects that can be expected for vitamins C and E in COVID-19 patients, in the present clinical study, these agents could not make a significant desired outcome compared to the control group while the only significant differences were the lower RR of the intervention group compared to the control group on days 4 and 8 as well as the lower lymphocyte count in the

Table 2. Comparison of vital signs and laboratory parameters between the groups in evaluated time points

Variable	Time	Group		*P* value
		Intervention (n = 38)	Control (n = 34)	
T (°C)	Day 4	36.90 ± 0.62	36.97 ± 0.55	0.103
	Day 6	36.86 ± 0.42	36.82 ± 0.32	0.811
	Day 8	36.74 ± 0.21	36.74 ± 0.27	0.818
	Discharge	36.80 ± 0.34	36.66 ± 0.36	0.204
PR (beats/min)	Day 4	84.11 ± 9.84	85.68 ± 7.65	0.206
	Day 6	83.67 ± 8.29	84.36 ± 6.54	0.287
	Day 8	84.50 ± 8.14	84.63 ± 5.74	0.579
	Discharge	80.92 ± 6.98	82.44 ± 3.98	0.171
RR (breaths/min)	Day 4	18.45 ± 1.06	19.91 ± 2.53	0.000
	Day 6	18.69 ± 1.55	19.00 ± 1.35	0.236
	Day 8	18.54 ± 1.40	19.44 ± 1.05	0.005
	Discharge	18.62 ± 1.58	18.81 ± 0.91	0.519
WBC (cells/mm^3)	Day 4	6326.32 ± 2169.15	6323.53 ± 3524.72	0.484
	Day 6	7025.81 ± 2532.85	7146.67 ± 2790.22	0.823
	Day 8	7200.00 ± 3749.40	7486.67 ± 2491.09	0.287
	Discharge	8000.00 ± 2883.14	6820.00 ± 1877.00	0.417
Neut. (% of WBC)	Day 4	64.96 ± 14.00	58.200 ± 12.38	0.026
	Day 6	64.46 ± 14.45	59.17 ± 10.76	0.090
	Day 8	70.42 ± 9.76	61.413 ± 9.025	0.021
	Discharge	67.22 ± 13.79	58.49 ± 9.33	0.033
Lymph. (% of WBC)	Day 4	26.99 ± 12.29	33.82 ± 10.58	0.019
	Day 6	26.24 ± 13.16	31.11 ± 9.04	0.100
	Day 8	20.66 ± 7.63	29.07 ± 7.79	0.014
	Discharge	23.40 ± 11.45	33.85 ± 7.94	0.007
Plt (cells/mm^3)	Day 4	283526.32 ± 313419.57	215823.53 ± 74192.41	0.262
	Day 6	262612.90 ± 83589.74	263666.67 ± 87661.71	0.914
	Day 8	307272.73 ± 85225.69	309733.33 ± 114969.85	0.897
	Discharge	333176.47 ± 97880.82	265133.33 ± 71027.02	0.043
O2 Sat. (%)	Day 4	93.368 ± 2.67	92.53 ± 2.73	0.119
	Day 6	93.30 ± 3.91	93.30 ± 2.98	0.257
	Day 8	92.83 ± 3.15	93.75 ± 2.62	0.508
	Discharge	94.85 ± 1.52	94.69 ± 1.96	0.937
LDH (U/L)	Day 4	548.37 ± 237.92	498.82 ± 165.44	0.969
	Day 6	554.16 ± 264.37	556.69 ± 225.61	0.638
	Day 8	604.57 ± 214.78	636.60 ± 286.70	1.000
	Discharge	466.25 ± 94.60	580.27 ± 266.60	0.295

intervention group on days 4 and 8 and discharge time. Our study showed, fewer treatment failures and shorter duration of hospital stay in the intervention group, although it was insignificant.

Conclusion

Based on the results, it seems that co-administration of vitamin C and vitamin E could not be a promising treatment option for COVID-19. In the future, further studies should be performed with well-established dosage and suitable numbers of patients. Moreover, in feature more clinical and paraclinical studies are needed to judge the role of these vitamins in COVID-19.

Limitations of the study

There are several limitations to this study, such as the relatively small sample size, lack of standardization of dosage antioxidants include vitamin C and vitamin E, and use of hydroxychloroquine as a national standard treatment regimen during the study period.

Accordingly, there are several variables that could affect the efficacy of vitamin C and vitamin E, such as the stage of diseases, the physiologic and psychological conditions of each patient and the level of oxidative stress agents.

Authors' contribution

AH, RS and ARM were the principal investigators of the study. AH and ARM were included in preparing the concept and design.

AR and MA revised the manuscript and evaluated the intellectual contents. MJT, SM and KD gathered data. All authors have read and approved the content of the manuscript and confirmed the accuracy or integrity of any part of the work.

Conflicts of interest

The authors declare that they have no competing interests.

Ethical issues

The research followed the tenets of the Declaration of Helsinki. The study was registered at the Iranian Registry of Clinical Trials (identifier: IRCT20180425039414N3; https://www.irct.ir/trial/48083). The ethics committee of Isfahan University of Medical Science (IUMS) approved this study with the record number of IR.MUI.MED.REC.1399.047. Written informed consent was obtained from all included patients. Moreover, ethical issues (including plagiarism, data fabrication, double publication) have been completely observed by the authors.

Funding/Support

This study was supported by a grant from Isfahan University of Medical Sciences (Grant #199017).

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