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Original Article

The Effect of a Low Dose of Vitamin C in Patients With COVID-19: A Double-Blind Randomized Controlled Trial

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Abstract

Background: Vitamin C is a micronutrient with anti-inflammatory and free radical scavenging properties that can strengthen the body's immune system. In this study, it was attempted to assess the clinical efficiency of oral vitamin C in treating COVID-19.

Materials and Methods: This double-blind randomized clinical trial was conducted on 401 patients hospitalized in Taleghani hospital, Abadan, over 18 years of age and with confirmed COVID-19 infection, from November 2020 to May 2021. The patients were randomly assigned to intervention groups (201 people, two tablets per day, each containing 500 mg of vitamin C) and the control group (200 people, placebo, containing starch received for five days). Improvements in clinical symptoms, death from baseline to the 28-day follow-up after the intervention, hospital length of stay, and laboratory values of C-reactive protein (CRP) were some of the considered outcome variables.

Results: No significant difference was observed between the two groups in terms of the daily improvement of clinical symptoms and the odds of healing from each symptom increased by about 48-50%. The difference in the length of hospital stay between the two groups was close to significant ($P=0.051$). There was no significant difference in mortality between the two groups ($P=0.8$). There was no difference between the two groups in the laboratory parameters, except for alkaline phosphatase ($P=0.03$).

Conclusion: Vitamin C had no significant effect on improving patients' clinical symptoms such as fatigue, fever, cough, and shortness of breath.

Keywords: Ascorbic acid, Hospitalized, COVID-19, Virus, Vitamin C

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Introduction

The coronavirus disease 2019 (COVID-19), which has affected millions of people around the world, has become a global health issue (1-3). As of July 9, 2022, 551 226 298 people had been infected with COVID-19, and 6 345 595 deaths have occurred accordingly (4).

The mechanism of COVID-19 in the body is associated with immune complications resulting from cytokine storms (5). The results of studies have shown that the reduction of cytokines and immunological damage can be an effective factor in the improvement of patients with COVID-19 (6).

During viral infections, micronutrients have a great effect on protecting the immune system (7). Vitamin C (ascorbic acid) is an essential micronutrient involved in various immune cellular functions (8). Vitamin C has been considered to reduce the pathogenicity of bacteria and viruses because it has antimicrobial properties (9).

Vitamin C is a micronutrient with anti-inflammatory and free radical scavenging properties. Various anti-inflammatory interventions such as steroids, vitamins and micronutrients, and immune-modulatory agents have been tried to date (9, 10).

In the review of systematic studies and various meta-analyses, due to the diverse methodology of the studies, there is considerable discussion on the use of vitamin C supplements (11). Currently, there are extremely few studies on the use of low-dose oral vitamin C for the treatment of COVID-19, and most studies have examined the effect of high doses of vitamin C for this purpose. This study sought to assess the clinical efficiency of oral vitamin C in improving the condition of patients with COVID-19.

Materials and Methods

Participants

This study was performed on 401 patients above 18 years of age who were referred to Taleghani hospital,

Abadan, Iran, from November 2020 to May 2021. Based on the World Health Organization's classification of the severity of COVID-19, patients with moderate, severe, and critical diseases were included in the study. Moderate disease included radiographic findings of pneumonia and $SpO_2 \geq 90\%$ on room air. In addition, severe disease included the pathognomonic radiographic findings of COVID-19 pneumonia plus one of the following: $SpO_2 < 90\%$ in room air, severe respiratory distress, respiratory rate (RR) > 30 breaths per minute, and critical diseases such as bilateral and the pathognomonic radiographic findings of COVID-19 pneumonia in association with either septic shock or acute respiratory distress syndrome (12).

According to eligibility criteria (Figure 1), 1112 patients were excluded, and 401 patients participated in this study. The inclusion criteria were patients whose laboratory results, including positive C-reactive protein (CRP) test or polymerase chain reaction tests, were positive for COVID-19 or whose computer tomography scans showed pulmonary involvement. Chest computer tomography images were validated by a trained radiologist.

On the other hand, the exclusion criteria included lactating and pregnant women, patients under 18 years of age, patients with kidney stones, diabetes, chronic renal failure, and urinary tract infections, and those requiring intubation on admission.

Study Design

This clinical trial was performed using randomized, placebo-controlled, double-blind methods. The randomization method was blocking randomization with blocks with a size of 4. Randomization sequence and concealment codes were created at www.sealedenvelope.com. Patients were randomly divided into intervention and control groups using block randomization. The intervention group consisted of 201 patients who received standard national protocol drugs + vitamin C in the amount of 1000 mg daily orally from the first day of inclusion (500 mg vitamin C every 12 hours for five days,

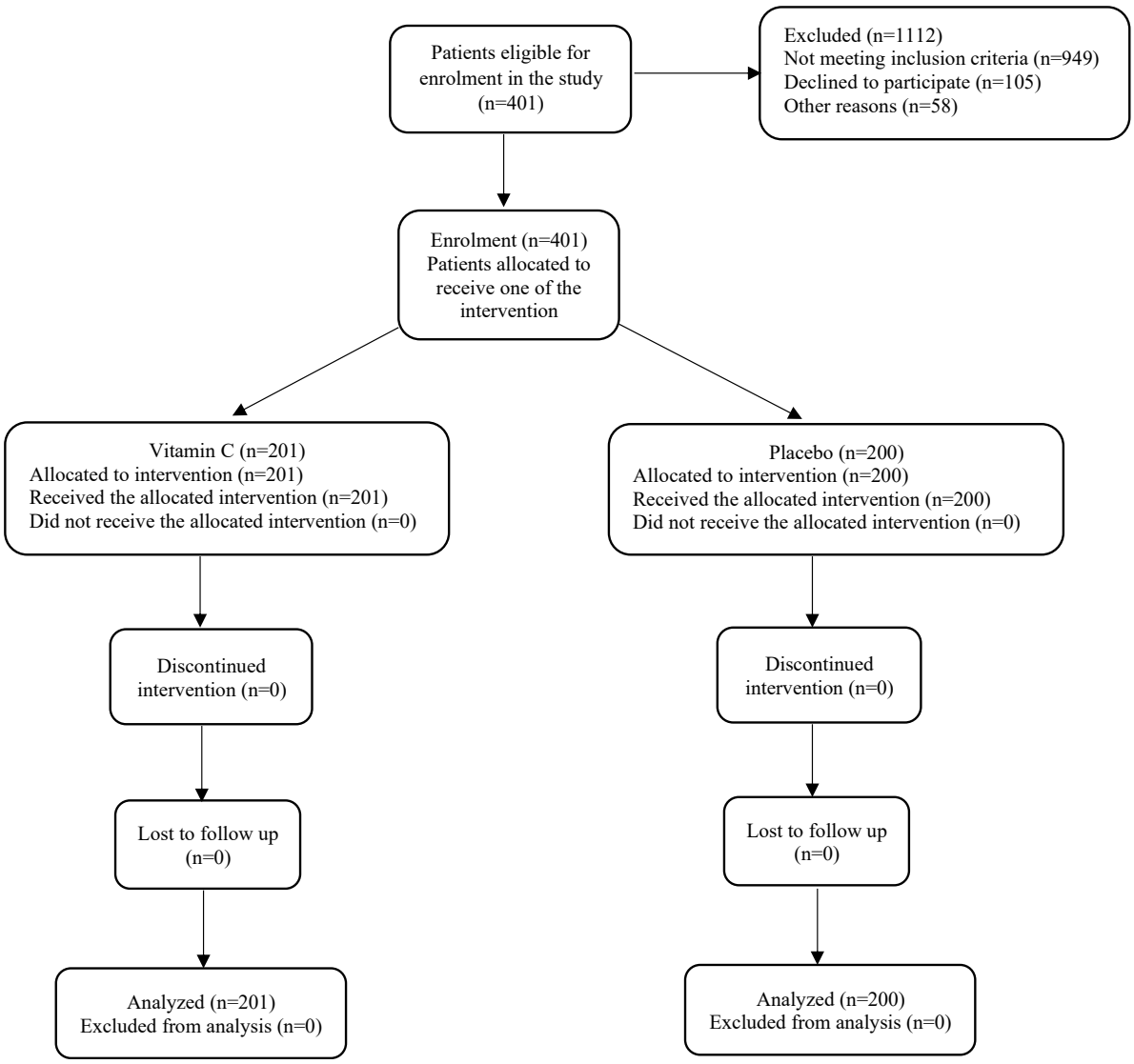

Figure 1. Patient Enrolment Process

Amivital). The control group consisted of 200 patients receiving standard national protocol drugs + vitamin C placebo every 12 hours for five days from the first day of inclusion. The placebo was produced to have a similar color, appearance, and taste as vitamin C by the Pharmacy School of Jundishapur University.

All participants were treated with the Iranian COVID-19 treatment protocol at the time of the study, which included oral lopinavir/ritonavir (Kaletra, Abbott Laboratories) 200/50 mg 2 tablets every 12 hours and a single stat dose of oral hydroxychloroquine (Tehran Daru) 400 mg on the first day of hospitalization.

Necessary explanations about the objectives of the study were given to the participants of this study, and they were told that they can discontinue the study at any time and can receive the standard treatment. The participants then gave their written informed consent.

Assessment of Variables

On the first day of hospitalization, sampling was conducted to measure the laboratory markers of the patients, including complete blood count (CBC), CRP, blood urea nitrogen (BUN), creatinine, Na, K, blood sugar, aspartate aminotransferase (AST), and alkaline phosphatase (ALP). The other laboratory markers were alanine transaminase (ALT), erythrocyte sedimentation rate (ESR), international normalized ratio (INR), venous blood gases pH (VBG pH), and venous blood gases HCO_2 (VBG HCO_2). On the discharge day, CBC and CRP were performed on patients.

Demographic information (age, gender, weight, and height of patients) and comorbidity were recorded as well. Patients' recovery status on the admission day, as well as 3, 5, and 10 days after the admission day, and upon discharge was determined by measuring RR, peripheral capillary oxygen saturation, cough, fatigue, core body temperature, and shortness of breath by trained nurses. Clinical recovery time and death were evaluated at the beginning and end of the intervention (day 5), as well as on days 7, 14, 21, and 28 after the intervention.

The duration of intensive care unit (ICU) hospitalization, duration of hospitalization in survivors, duration of intensive mechanical ventilation, and days of treatment initiation to death were evaluated as well.

Side Effects

The oral consumption of vitamin C up to 2 grams per day does not cause complications (13), but gastrointestinal complications may occur in higher doses. In this study, 1 gram of oral vitamin C daily was used; however, no adverse effects were observed based on the results.

Clinical Improvement

In this study, patients' recovery concerning the improvement of clinical symptoms (The absence of fever, lack of shortness of breath, lack of cough or improvement, and no fatigue or improvement for 24 hours) from the start of drug therapy was evaluated, and the New Early Warning System (NEWS) criterion was also used to examine patients' recovery.

NEWS is a standard clinical scoring system based on six physiological parameters, including systolic blood pressure, oxygen saturation, pulse rate, RR, level of consciousness, and body temperature, which is employed to diagnose disease severity, particularly in patients with COVID-19 (14).

Clinical risk can be identified from the total score obtained from the above-mentioned parameters. A total score of 0-4 indicates low clinical risk, and a score of 3 per individual parameter represents low-moderate clinical risk. In addition, a total score of 5-6 demonstrates moderate clinical risk, and a total score of 7 or more indicates high clinical risk.

In this study, patients' recovery was also evaluated using the NEWS. Our criteria for patients' recovery and low clinical risk was a score of 0-4 for 24 hours. The conditions of patients in terms of deterioration and improvement were examined using the NEWS scores at the beginning of admission, on the fifth day, and on the day of discharge.

Outcomes

The primary outcome was the patients' recovery concerning improvements in clinical symptoms (The absence of fever, lack of shortness of breath, lack or improvement of cough, and absence or improvement of fatigue for 24 hours) from starting the trial medications.

The secondary outcomes were death from baseline to follow-up 28 days after the intervention, hospital length of stay, duration of invasive mechanical ventilation (IMV), ICU length of stay, laboratory values of CRP, and evaluation of patients' recovery time based on their NEWS scores.

Statistical Analysis

In this study, descriptive statistics, including the mean (SD), median (Interquartile range), and graphical methods, have been used to describe the recruited individuals. For continuous variables, the normality of the distribution was assessed using the Shapiro-Wilk test. The baseline characteristics between the intervention and control groups were compared using an independent sample *t* test and Mann-Whitney U test for continuous covariates and a chi-square test for categorical covariates. Laboratory parameters were compared between admission and discharge days using the related samples Wilcoxon signed rank test in each group separately. Comparisons were then made between the two groups after adjusting for the effects of age and gender using an analysis of covariance. Clinical symptoms with multiple

measurements were compared between the two groups by calculating the odds ratio (95% CI) for categorical covariates and mean differences for continuous covariates using generalized estimating equations (GEE) methods. NEWS scores were compared between the two groups at each time point separately using chi-square and Fisher's exact tests. Time to discharge from the ICU was portrayed and compared using the Kaplan-Meier method and the log-rank test, respectively. All analyses were performed using SPSS statistical software (version 21) at a 0.05 level of significance.

Results

In this study, 401 people with COVID-19 participated, 200 of whom received a placebo and the remaining 201 cases received vitamin C. Baseline characteristics, outcomes, and comorbidity are presented in Table 1. The mean (SD) age of the vitamin C group was 47.28 (14.63) with a range of 61 years and that of the control group was 45.66 (14.13) with a range of 67 years ($P=0.32$). No significant difference was observed in terms of gender ($P=0.24$) or body mass index ($P=0.69$) between the two groups.

Of the 401 patients in the study, 18 (4.48%) cases died during hospitalization [14 (77.7%)] and the follow-up period [4 (22.2%); follow-ups were performed on days 7, 14, 21, and 28 after the intervention]. Out of 14 people who died while being hospitalized, 3 people were in the ICU, and 11 people were hospitalized in the other wards. There was no significant difference in mortality between the two groups ($P=0.8$). The difference in the length of hospital stay between the two groups was close to significant ($P=0.051$).

Except for obesity ($P=0.03$), there were no statistically significant differences between the two groups in terms of comorbidity ($P>0.05$, Table 1).

The laboratory parameters of hemoglobin (Hgb), platelet (Plt), white blood cell (WBC), polymorphonuclear leukocyte (PMN), lymph, and CRP were tested at two time points (upon admission and discharge) and are presented in Table 2. There was no difference between the two groups in the parameters of Hgb, WBC, or PMN at the time of discharge, but the lymphocyte increased during the follow-up in both groups. This increase was greater in the placebo group, and the mean in the placebo group was higher at the time of discharge, although this difference was not significant ($P=0.052$). Similarly, the

Table 1. Baseline Characteristics, Outcomes, and Comorbidity

Variables	Vitamin C (201)	Placebo (200)	*P* Value
Age (year), mean (SD)	47.28 (14.63)	45.66 (14.13)	0.32
Male, n (%)	109 (54.2)	120 (60)	0.24
BMI, mean (SD)	13.34 (2.24)	13.23 (1.69)	0.56
Smoking, n (%)	15 (7.5)	4 (2)	0.01
Positive PCR, n (%)	191 (95)	191 (95.5)	1.00
Hospital length of stay (day), median (IQR)	5 (2)	5 (2)	0.051
Death from baseline to follow-up 28 days after the intervention, n (%)	8 (3.9)	10 (5)	0.8
Admission to ICU entry (n)	8	6	0.79
Discharge from ICU, n (%)	6 (3)	5 (2.5)	1.00
Death in ICU, n (%)	2 (0.99)	1 (0.5)	1.00
ICU length of stay (day), median (IQR)	5 (10)	8 (4)	0.34
Duration of hospitalization in (day), median (IQR)	8 (15)	14 (7)	0.28
Admission to IMV n (%)	1 (0.49)	0 (0)	1.00
Duration of IMV, median (IQR)	2 (0)	-	-
comorbidity			
Obesity, n (%)	9 (4.5)	2 (1)	0.03
Chronic cardiac disease, n (%)	14 (7)	5 (2.5)	0.057
COPD, n (%)	2 (1)	1 (0.5)	1.00
Asthma, n (%)	10 (5)	4 (2)	0.11
A chronic neurological disorder, n (%)	5 (2.5)	2 (1)	0.45
Chronic hematologic disease, n (%)	2 (1)	2 (1)	1.00
Hypertension, n (%)	12 (6)	9 (4.5)	0.51
Liver disease, n (%)	4 (2)	0 (0)	0.12
Other risk factors, n (%)	12 (6)	9 (4.5)	0.51

Note. SD: Standard deviation; BMI: Body mass index; IQR: Interquantile range; PCR: Polymerase chain reaction; ICU: Intensive care unit; IMV: Invasive mechanical ventilation; COPD: Chronic obstructive pulmonary disease.

Plt parameter increased in both groups during the follow-up period. This increase was greater in the vitamin C group, and the mean in the vitamin C group was higher than the placebo group at the time of discharge, although this difference was not significant ($P=0.096$).

A comparison of the CRP values between baseline and the discharge day in each group revealed no change in the placebo group ($P=0.4$), while a decrease was observed in the vitamin C group, which was not significant ($P=0.055$). In the comparison of the last measurement of CRP, no significant difference was found between the two groups ($P=0.48$).

As illustrated in Figure 2, there were no significant differences between the two treatments at baseline regarding laboratory parameters, including BUN, Na, K, ESR, VBG HCO_2, creatinine, blood sugar, AST, ALT, INR,

Table 2. Laboratory Parameters Tested at Two Time Points (Upon Admission and Discharge)

			Baseline	Last Measurement	*P* Value[a]	Difference Between Vitamin C-Placebo	*P* Value[b]
			Mean (SD)	Mean (SD)			
Hgb	Placebo		13.23 (1.69)	13.17 (1.77)	0.52	0.14	0.69
	Vitamin-C		13.34 (2.24)	12.98 (2.04)	0.004	(-0.58,0.88)	
Platelet	Placebo		222.89 (95.54)	279.70 (123.76)	<0.001	24.51	0.096
	Vitamin-C		234.21 (80.93)	311.71 (117.43)	<0.001	(-4.38,53.41)	
WBC	Placebo		7.33 (4.59)	8.64 (4.35)	0.7	1.16	0.18
	Vitamin-C		7.44 (3.98)	9.79 (4.3)	0.03	(-0.55,2.86)	
PMN	Placebo		71.94 (16.82)	67.62 (17.96)	0.028	2.33	0.4
	Vitamin-C		75.11 (11.23)	70.53 (15.08)	0.007	(-2.64,6.58)	
Lymph	Placebo		19.27 (13.15)	21.91 (14.28)	0.089	-3.12	0.052
	Vitamin-C		18.19 (10.38)	18.62 (10.10)	0.97	(-6.28, 0.027)	
CRP	Placebo	Negative	3 (2.42)	2 (2.82)	0.4	0.48[c]	
		Trace	17 (13.71)	19 (26.76)			
		1+	49 (39.52)	22 (30.99)			
		2+	20 (16.13)	9 (12.68)			
		3+	31 (25)	19 (26.76)			
		4+	4 (3.23)	0 (0)			
	Vitamin-C	Negative	1 (0.68)	2 (2.27)	0.055		
		Trace	14 (9.59)	25 (28.41)			
		1+	56 (38.36)	29 (32.95)			
		2+	35 (23.97)	12 (13.64)			
		3+	38 (26.03)	16 (18.18)			
		4+	2 (1.37)	4 (4.55)			

Note. SD: Standard deviation; Hgb: Hemoglobin; WBC: White blood cell; PMN: Polymorphonuclear leukocyte; CRP: C-reactive protein.
[a] The *P* value based on related-samples Wilcoxon signed rank test for comparing baseline and last measurement.
[b] The *P* value for the difference between the two groups in the last measurement after adjusting for baseline measurements, age, and gender using the analysis of covariance.
[c] *P* value based on Fisher's exact test for comparing the last measurement between the two groups.

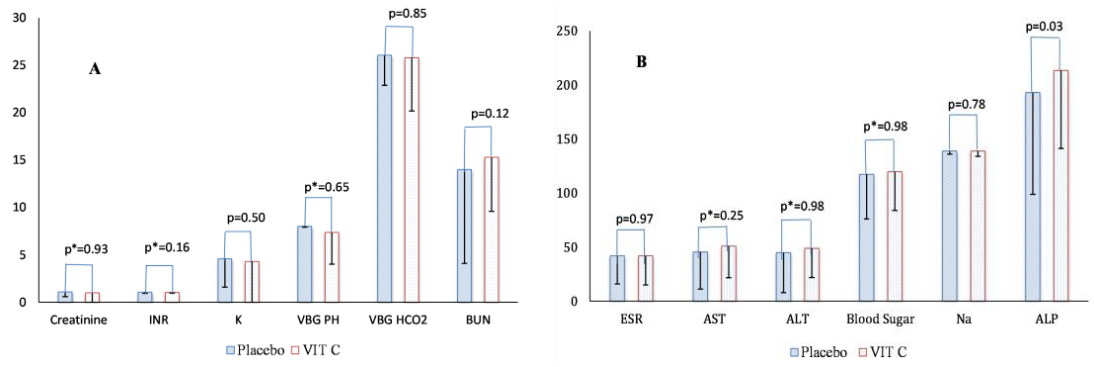

Figure 2. Laboratory Parameters Tested Upon Admission. *Note*. INR: International normalized ratio; VBG PH: Venous blood gases PH; BUN: Blood urea nitrogen; ESR: Erythrocyte sedimentation rate; AST: Aspartate aminotransferase; ALT: Alanine transaminase; ALP: Alkaline phosphatase

and VBG PH. However, the mean ALP was significantly higher in the vitamin C group ($P=0.03$, Figure 2).

The patient's status regarding clinical symptoms on the admission day and during follow-ups on days 3, 5, and 10, as well as upon discharge, are presented in Table 3. As time increased from initial treatment, the proportion of patients without fatigue, fever, cough, and shortness of breath increased significantly. Each day, the odds of healing from each symptom increased by about 48% to 50%, but no significant difference was observed between the two groups (Table 3). In contrast, for each day, after the initial treatment, no significant change was found in RR or SPO_2. In addition, no significant difference was observed between the two groups during the study period (Table 3).

Patients with different NEWS scores (with each group scored for each of the three measurement times) are depicted in Figure 3. The proportion of patients with higher NEWS scores (indicating higher clinical risk) decreased in the second and third measurements. On the other hand, the proportion of patients with lower NEWS scores (indicating low clinical risk) represented an increase. The GEE analysis of NEWS ordinal responses showed that the ORs of having a lower NEWS score in the second and third measurements than in baseline measurements were 3.07 and 3.3, respectively. However, there was no significant difference between the vitamin C and placebo groups (OR = 0.91, 95% CI: 0.63-1.3, $P=0.6$).

Discussion

The findings of this study revealed that the administration of oral vitamin C for five days did not significantly improve the clinical symptoms of patients with COVID-19 when compared to the placebo group. There was no statistically significant difference between the groups in the outcomes of mortality, hospital length of stay, duration of IMV,

Table 3. Comparing Clinical Symptoms on Admission Day and Days 3, 5, and 10, as well as Upon Discharge

With Symptoms		Measurement					Time Effect	Group Effect
		1st	3rd	5th	10th	Discharge Day		
Fatigue	Placebo	82 (41.21)	143 (71.5)	116 (83.45)	43 (89.58)	5 (62.5)	1.48 (1.28, 1.71)	1.09 (0.81, 1.46)
	Vit-C	79 (39.3)	152 (75.62)	123 (84.83)	66 (94.29)	6 (85.71)		
Fever	Placebo	136 (68.69)	178 (89)	129 (92.81)	46 (95.83)	8 (100)	1.5 (1.31, 1.71)	0.94 (0.72, 1.42)
	Vit-C	144 (72)	171 (85.5)	135 (93.75)	69 (98.57)	6 (85.71)		
Cough	Placebo	57 (28.64)	123 (61.5)	98 (70.5)	39 (81.25)	8 (100)	1.48 (1.37, 1.6)	0.79 (0.59, 1.08)
	Vit-C	57 (28.36)	94 (46.77)	102 (70.34)	59 (84.29)	7 (100)		
Shortness of breath	Placebo	55 (27.5)	132 (66)	104 (74.82)	43 (89.58)	6 (75)	1.52 (1.34, 1.71)	1.05 (0.78, 1.41)
	Vit-C	63 (31.5)	122 (60.7)	116 (80)	64 (91.43)	6 (85.71)		
RR	Placebo	21.24 (4.84)	20.97 (4.85)	20.71 (2.63)	21.02 (2.25)	22.13 (2.85)	0.01 (-0.06,0.08)	-0.07 (-0.68,0.53)
	Vit-C	21.29 (2.58)	20.71 (2.65)	20.96 (3.52)	20.70 (3.71)	19.86 (4.85)		
Sp_{O2}	Placebo	94.50 (3.78)	95.12 (3.85)	95.53 (3.85)	94.96 (4.50)	95.75 (1.91)	0.06 (-0.06,0.17)	-0.04 (-0.72,0.63)
	Vit-C	94.63 (3.73)	94.82 (4.37)	95.35 (4.04)	95.90 (3.87)	91.57 (15.74)		

Note. Vit-C: Vitamin C; RR: Respiratory rate.

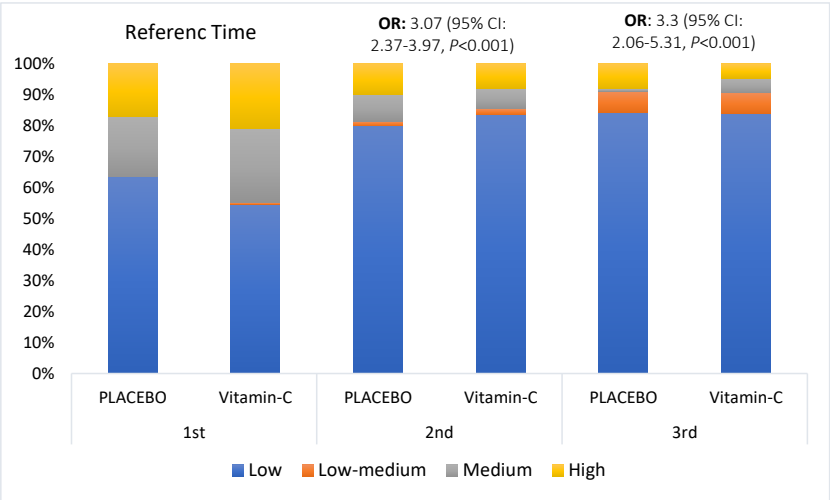

Figure 3. NEWS Scores of Patients (With Each Group Scored for Each of the Three Measurement Times). *Note*. NEWS: New Early Warning System; OR: Odds ratio; CI: Confidence interval; £: Fisher's exact test; Ω: Chi-square test

ICU length of stay, or laboratory values of CRP. The results of this study also showed that taking vitamin C had no adverse effects.

One of the good features of this study was its large sample size, and patient survival data were collected on days 7, 14, 21, and 28 post-intervention. Moreover, the serum levels of inflammation were measured in the present study. Additionally, despite the usual method of assessing the improvement of clinical symptoms, in this study, another method (NEWS scores) was used to evaluate the clinical conditions of patients.

Severe COVID-19 infection causes pulmonary and systemic inflammatory responses; due to the anti-inflammatory properties of vitamin C, this micronutrient reduces the excessive immune response in this disease (15).

In the study by Xia et al, it was observed that in patients with severe COVID-19, high-dose vitamin C reduces the level of inflammatory markers, thus it has the potential benefit of reducing hyper-inflammation (16).

A daily intake of about 200-400 mg of vitamin C meets the body's needs in healthy people. However, in the disease condition, more consumption is required to maintain sufficient levels of vitamin C in the body (17).

Vitamin C is generally safe and well tolerated. In high doses of 2 grams per day for adults, some studies reported a risk for gastrointestinal disorders and kidney stones (18).

In the present study, a daily dose of 1000 mg was prescribed for 5 days in patients with COVID-19 (to prevent the adverse side effects of vitamin C) and possible side effects underwent investigation.

The effects of vitamin C in the treatment of this disease are controversial according to the studies.

Fowler et al found that compared to a placebo, vitamin C supplementation (50 mg/kg, every 6 hours for 96 hours, IV) in patients with acute respiratory distress syndrome and sepsis did not affect the disease severity and CRP levels (19).

Majidi et al performed a clinical trial on 120 patients with COVID-19. In this study, 500 mg of oral vitamin C was administered daily for 14 days. The mean survival duration of patients in the vitamin C group was longer than that of the control group. However, vitamin C did not affect the laboratory factors such as arterial blood gas, CBC, partial thromboplastin time, Hgb, and Plt. In the present study, vitamin C intake had no effect on any laboratory factors, except for ALP (20).

In a clinical trial by Zhang et al, 56 patients with COVID-19 infection were given 50 mL of vitamin C every 12 hours for seven days. Vitamin C did not affect the patient's condition improvement, hospital mortality, or hospital stay (21), which is in accordance with the results of our research.

In another clinical trial study conducted on 60 patients with severe COVID-19 who received vitamin C 6 grams per day (high dose), no improvement was observed in the results (22).

Darban et al performed a pilot randomized trial on 20 patients with severe COVID-19. Patients were given oral melatonin, vitamin C (2 g, q6 hours, IV), and oral zinc sulfate for 10 days. This treatment did not result in a considerable improvement in the clinical status, length of ICU stays, or inflammatory marker levels (23).

This study has some limitations. First, the use of low doses of vitamin C in this study, due to the critical condition of the patients, we were unsure about the safety of high doses of vitamin C. Secondly, the study did not measure the serum level of vitamin C before the study, and the patient's condition in terms of vitamin C was unknown. Accordingly, further research is recommended to better evaluate the results by means of diverse doses of vitamin C over a longer period of time.

Conclusion

Vitamin C had no significant effect on improving the clinical symptoms of patients, including fatigue, fever, cough, and shortness of breath. Therefore, the use of low doses of vitamin C had no effect on improving the clinical symptoms of patients with COVID-19.

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Authors' Contribution

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Writing–review & editing: Esmat Radmanesh, Sajedeh Mousaviasl, Bagher Pahlavanzade.

Competing Interests

The authors declare that they have no conflict of interests regarding the publication of this study.

Disclaimer

This article doesn't have prior publication or presentation in a conference/seminar.

Ethical Approval

The protocol of this study was approved by Abadan Medical Sciences Ethics Committee with the ethics code IR.ABADANUMS.REC.1398.119. The trial was conducted in accordance with the principles of the Declaration of Helsinki and registered in the Iranian Registry of Clinical Trials (www.irct.ir) on April 4, 2020 (identifier: IRCT20200324046850N5; https://www.irct.ir/).

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Informed Consent

All participants gave their written informed consent after receiving explanations regarding the study objective and methodology.

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