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LETTER TO EDITOR

High-Dose Vitamin C in the Treatment of Covid-19 Patients in Intensive Care Unit; A Letter to the Editor

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Dear Editor

The COVID-19 pandemic has caused a worldwide panic. Until 5 March 2023, over 759,000,000 COVID-19 cases with over 6,800,000 deaths have been confirmed worldwide (1-5). The patients primarily suffer from fever and cough, shortness of breath, and myalgia (4-7). Vitamin C is a powerful antioxidant, which helps to improve the body's immune system. The antioxidant property of vitamin C reduces inflammation and improves the body's defense function against pathogens (8, 9). Given the above notion, we investigated the efficacy of high-dose vitamin C on critically ill COVID-19 patients admitted to the intensive care units and evaluated its impact on patients' outcomes, such as mortality, O2 saturation, and the hospital length of stay (LOS). The protocol of this study was registered in the Iranian registry of clinical trials under the ID of IRCT20210714051891N1. This trial was conducted on 210 COVID-19 patients hospitalized in the ICU of Imam Reza General Hospital, Tabriz, Iran from October 7, 2021, to March 6, 2022. Adult patients aged 18 years or over who suffered from COVID-19 ((positive for SARS-CoV-2 by reverse transcription polymerase chain reaction (RT-PCR) evaluation by nasopharyngeal swabs)) and had respiratory failure (PaO2/FiO2 on ICU admission <300 mmHg) were included in the trial. Exclusion criteria were having any previous history of vitamin C allergy, pregnant or lactating women, severe cardiogenic pulmonary edema, patients with less than 24 hours survival time, and patients with comorbidities like the need for renal replacement therapy, end-stage malignancy, G-6-PD deficiency, or diabetic ketoacidosis. Patients were included in the study during the first 12 hours after admission to the ICU and, then, were randomly assigned to two groups (i.e., treatment and control groups) using the Excel software. The intervention group received vitamin C in addition to the standard protocol for seven days. 12 g of vitamin C was injected via a pump within four hours, and this treatment procedure was repeated every 12 hours. Therefore, the total vitamin C dose for the treatment group was 24 g per day (240 cc)(10). Both study groups received Remdesivir based on the WHO guideline (i.e., 200 mg on the first day and then 100 mg/day for the next four days) as well as Dexamethasone/Methylprednisolone, antipyretics, and stress ulcer prophylaxis. The sample size was determined to be 105 individuals for each of the intervention and control groups (n=210) based on the data from previous studies (10-12), and by considering the values of indices =0.05 (type 1 error), power of 80%, P1=0.379, and P2=0.222. G*Power 3.0.10 Software was used to compare the ratio difference between the two populations. The data were analyzed using SPSS 22 software, and the results were reported as frequency (percentage) and median (interquartile range). Kolmogorov-Smirnov test was used to test the normality of the data distribution. Chi-square tests, Fisher Exact test (if necessary), and Mann-Whitney U Test (for non-normal data) were used to analyze the data. A P<0.05 was considered as the significance level. Patients' demographic and clinical characteristics are shown in Table 1. The most underlying disease in both groups was hypertension (HTN), followed by diabetes. The two study groups were compared regarding the underlying disease, but no statistically significant difference was detected between them (p = 0.197). Table 2 shows the outcome of patients regarding mortality, hospital discharge, and discharge with personal consent. The results showed the number of patients in each group that were discharged from the hospital alive at the end of the study and were not unwilling regarding the continuation of the study. In the intervention group, 87 patients were treated with high-dose

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corticosteroids, 16 patients were treated with Tocilizumab, and two patients were treated with both corticosteroids and Tocilizumab. In the control group, 85 patients were treated with high-dose corticosteroids, 15 patients were treated with Tocilizumab, and five patients were treated with both corticosteroids and Tocilizumab which showed no statistically significant difference (p = 0.32). The mortality rate was reported in 63 patients in the control group and 66 patients in the group receiving vitamin C (p = 0.747). Comparing the variables related to the respiratory factors revealed no statistically significant difference between the two groups regarding the percentage of pulmonary involvement and O2 saturation (p = 0.148 and p = 0.591, respectively). There was no statistically significant difference between the groups regarding the serum D-dimer, lactate dehydrogenase, Ferritin, and erythrocyte sedimentation rate (p > 0.05). The median c-reactive protein level (CRP) in the group receiving vitamin C was lower than that in the control group (p = 0.025; Table 2).

Taking into account the pathophysiology and theoretical background, initial reports, and results from previous studies, it is recommended that further studies be carried out to assess the effect of vitamin C administration in treating patients with COVID-19 (13).

1. Declarations

1.1. Acknowledgments

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1.2. Funding

Research deputy of Tabriz University of Medical Sciences.

1.3. Authors' contribution

"MB, HA, AM (second author), and HS performed the data collection, literature review, and drafting of the manuscript. HS, AMK (4th Author), and MB undertook the major parts of the study design and performed the statistical analysis. All authors read and approved the manuscript.

1.4. Ethics Approval and Consent to Participate

This study was approved by the regional ethics committee with No. IR.TBZMED.REC.1400.519. and registered in IRCT with IRCT registration number: IRCT20210714051891N1. Written informed consent was obtained from the patients and their relatives. All methods were implemented in accordance with the relevant guidelines and regulations. Furthermore, all procedures in the study involving human participants were performed in accordance with the ethics standards of the institutional/national research committee and with the Helsinki Declaration and its later amendments or comparable ethics standards.

1.5. Consent for Publication

The data presented in the manuscript and its supplemental files included no details on the patients and, thus, no consent was required for publication.

1.6. Availability of Data and Materials

The datasets generated and analyzed during the current study are not publicly available due to restriction of ethic committee of Tabriz University of Medical Sciences but are available from the corresponding author upon reasonable request.

1.7. Competing Interests

The authors declare that they have no conflict of interests.

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Table 1: Comparing the baseline characteristics of patients between groups

Variable	Groups		P-value
	Vit C (n=105)	Control (n=105)	
Sex			
Male	52 (49.5)	66 (62.9)	0.052
Female	53 (50.5)	39 (37.1)	
Age (year)			
Median (IQR)	60 (48 - 67.5)	65 (51 - 75)	0.068
Comorbidities			
No	52 (49.5)	39 (37.1)	0.197
Diabetes mellitus	4 (3.8)	6 (5.7)	
Hypertension	13 (12.4)	20 (19)	
Hyperlipidemia	0 (0)	1 (1)	
Ischemic Heart Disease	4 (3.8)	2 (1.9)	
Immune disorder	4 (3.8)	1 (1)	
Rheumatoid Arthritis	1 (1)	0 (0)	
Cancer	2 (1.9)	4 (3.8)	
Chronic Kidney Disease	0 (0)	3 (2.9)	
Other*	25 (23.8)	29 (27.6)	
Past medical history			
Corticosteroid	5 (4.8)	3 (2.9)	0.145
Chemotherapy	0 (0)	4 (3.8)	
No	100 (95.2)	98 (93.3)	
APACHE			
Median (IQR)	14 (10 - 20)	16 (11 - 23)	0.055
Duration of hospitalization			
Median (IQR)	5 (4 - 9)	5 (3 - 7)	0.111
Habit			
Smoker	4 (3.8)	4 (3.8)	1.000
Alcohol	1 (1) 4 (3.8)	0.369	
Vaccinated			
Yes	3 (2.9)	2 (1.9)	1.000
No	102 (97.1)	103 (98.1)	
laboratory findings (admission to ICU)			
D-Dimer	2135 (957.5 - 5387.5)	1810 (828.5 - 4693.5)	0.397
CRP	75 (36.5 - 132)	95 (47 - 146.5)	0.025
Lactate dehydrogenase	870 (534.5 - 1209.5)	690 (495.5 -1245.5)	0.280
Ferritin	663 (455 - 790)	760 (522.5 - 926)	0.087
ESR	40 (20.5 - 55)	45 (20.25 - 66.5)	0.347
O2 saturation (%)			
Median (IQR)	83 (72 - 89.5)	80 (70 - 89.5)	0.591
Lung involvement (%)			
Median (IQR)	70 (50 - 80)	70 (50 - 80)	0.418

Data are presented as frequency (%) or median (interquartile range (IQR)). *Other diseases in each disease group were so small and rare that they are not listed separately in the table. ESR: Erythrocyte sedimentation rate; CRP: C-reactive protein; ICU: intensive care unit.

Table 2: Comparing the studied outcomes between groups

Outcome	Groups		P-value
	Vit C (n=105)	Control (n=105)	
Disposition			
Death	66 (62.9)	63 (60)	
Discharge	33 (31.4)	39 (37.1)	0.747
Discharge by personal consent	6 (5.7)	3 (2.9)	