Original Article

High-dose Intravenous Vitamin C in Early Stages of Severe Acute Respiratory Syndrome Coronavirus 2 Infection: A Double-blind, Randomized, Controlled Clinical Trial

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Abstract

Objective: Based on previous studies in the sepsis population, Vitamin C could prevent injuries when administered in high doses and before the damage is established. This study aimed to evaluate the protective potentials of high-dose Vitamin C in the progression of coronavirus disease 2019 (COVID-19). **Methods:** A double-blind, placebo-controlled clinical trial was conducted. Patients with moderate-to-severe disease severity based on the World Health Organization definition were enrolled and received 12 g/d Vitamin C (high-dose intravenous Vitamin C [HDIVC]) or placebo for 4 days. Sequential Organ Failure Assessment (SOFA) score as a primary outcome, National Early Warning Score, Ordinal Scale of Clinical Improvement, and cytokine storm biomarkers were recorded on days 0, 3, and 5. Survival was also assessed on day 28 after enrollment. **Findings:** Seventy-four patients (37 patients in each group) were enrolled from April 5, 2020, to November 19, 2020, and all patients completed follow-up. A lower increase in SOFA score during the first 3 days of treatment (+0.026 vs. +0.204) and a higher decrease in this parameter in the last 2 days (−0.462 vs. −0.036) were observed in the treatment group. However, these differences did not reach a significance level ($P = 0.57$ and 0.12, respectively). Other indices of clinical and biological improvement, length of hospitalization, and intensive care unit admission days were the same between the two groups. Treatment did not affect the 28-day mortality. **Conclusion:** Among patients with moderate-to-severe disease of COVID-19, the use of HDIVC plus standard care resulted in no significant difference in SOFA score or 28-day mortality compared to the standard care alone.

Keywords: *Coronavirus disease 2019, high-dose Vitamin C, inflammation, severe acute respiratory syndrome coronavirus 2*

Introduction

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection is characterized by mild symptoms at the initial viral phase and can progress to severe multi-organ dysfunction at the inflammatory

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phase. Viral replication is responsible for the first occurring symptoms, and organ dysfunction is due to immunopathologic events. Previous studies have shown that clinical outcome is more related to the severity of inflammatory responses than viral load.[1,2] Since no effective treatment for each phase is available,[3-5] finding a new therapeutic strategy can save millions of lives.

High-dose intravenous Vitamin C, which has anti-inflammatory and antioxidant properties, has been recently expressed as adjunctive therapy in inflammatory conditions such as sepsis. The potential benefits of ascorbic acid can be classified into three domains: indirect antiviral activity, immune-modulating effects of Vitamin C on innate and adaptive immunity, and potent antioxidant properties.[6-8]

As SARS-CoV-2 infection is accompanied by endothelial and epithelial damage,[2,9] cytokine storms, micro- and macrothrombosis, and multi-organ failure,[10] it is hypothesized that early administration of Vitamin C can prevent this process due to its potential benefits.[11] Fisher *et al*. found that high-dose intravenous Vitamin C (HDIVC) reduces acute lung injury in animal models of acute respiratory distress syndrome (ARDS).[12,13] Furthermore, in one study on patients in the early stages of sepsis, Sequential Organ Failure Assessment (SOFA) score, C-reactive protein (CRP), and thrombomodulin levels were decreased dose dependently without any adverse effect.[14] In contrast to a former study, HDIVC in later stages of sepsis showed no clinical improvement.[15] These findings suggest that the therapeutic efficacy of HDIVC is diminished in the late phase of illness, and no more benefit is seen. Therefore, the right time of administration is the matter.

Beyond non-coronavirus disease studies, intravenous administration of 6 g/day of Vitamin C in coronavirus disease 2019 (COVID-19) patients with mild-to-severe disease severity did not show any beneficial effects except for higher SpO2 at discharge.[16] Nevertheless, 24 g/day of Vitamin C for 7 days in critically ill COVID-19 patients showed a significantly higher PaO_2/FiO_2 (PF) ratio, signs of improvement in SOFA score, and 28-day mortality.[1] Vitamin C supplementation with high-dose zinc in ambulatory patients could not shorten the duration or severity of symptoms.[17]

Considering the results of previous studies, the present trial aimed to assess whether early administration of HDIVC in patients with moderate-to-severe COVID-19 can inhibit the progression of the disease.

Methods

The ethics committee approved the protocol of this randomized, double-blind, placebo-controlled clinical trial at Tehran University of Medical Sciences (IR.TUMS.VCR.REC.1399.0056). It was submitted to the Iranian Registry of Clinical Trials on March 31, 2020 (IRCT20190917044805N2). The written informed consent was obtained in line with local processes. Patient enrollment was performed based on inclusion and exclusion criteria in a university hospital (affiliated with Tehran University of Medical Sciences) from April 5, 2020, to November 19, 2020.

Patients over 18 years old had confirmed COVID-19 infection (based on polymerase chain reaction or chest computed tomography [CT]) and met the criteria for moderate-to-severe disease based on the World Health Organization (WHO) definition.[4] They were included if they showed radiographic changes in favor of SARS-CoV-2 infection in chest X-ray, CT scan, or tachypnea (more than 30 breaths/min); or severe respiratory distress; or SpO2 <90% on room air and agreeing to participate. Exclusion criteria were participation in other clinical trials, an expectation of invasive mechanical intubation during 48 h, previous experience of allergy to Vitamin C, estimated glomerular filtration rate (GFR) <30 mL/min (based on Cockcroft-Gault equation), active nephrolithiasis, pregnancy or lactation, documented diagnosis of cancer, history of glucose-6-phosphate dehydrogenase (G6PD) deficiency, and interstitial lung disease and more than 1 g/day intake of Vitamin C supplement in the last 7 days.

This study was conducted in a double-blind process. Patients, investigators, health-care workers (nurses and physicians), and statistical analyzers were blinded by Block randomization using four blocks. A table of patient numbers and block randomization codes was created by an online randomization web page (https://www.sealedenvelope.com) and presented to the pharmacist who was in-charged of infusion bag preparation and had no role in data gathering and result interpretation. The investigator and the serum ingredient informed that the patient's number had been determined by the pharmacist based on the randomization table. Vitamin C and placebo IV admixtures were colorless and not differentiable based on container appearance.

The pharmacist in charge randomly allocated patients to the treatment or placebo group. Patients in the treatment group received 12 g/day of Vitamin C (500 mg/5 mL ampule supplied from Darupakhsh Pharmaceutical Chemical Company). To prepare the Vitamin C intravenous admixture, the contents of 24 ampules were dissolved in dextrose 5% (total volume: 200 ml). This content was infused each day for over 12 h for 4 days.

Patients in the placebo group received 200 mL dextrose 5% daily for 4 days. According to stability studies,[18,19] the content of prepared admixtures is 99% stable at room air temperature for 24 h.

Considering the long recruitment period and the lack of effective treatment for COVID-19, the institute's routine treatment protocol varies over time during the study. Patients were not deprived of the usual care after enrollment in the study. Hydroxychloroquine, lopinavir/ritonavir, atazanavir/ritonavir, sofosbuvir/daclatasvir, and remdesivir were the medications administered to affect viral replication. We considered all of these agents antiviral in the data gathering. Dexamethasone and methylprednisolone were administered to alleviate the inflammatory phase. Treatment with these agents was recorded for each patient to assess the equality of treatment between groups in the later analysis. Noninvasive and invasive mechanical ventilation was applied for each patient based on the clinical scenario.

High-dose Vitamin C has been used for decades and is considered safe at 1.5 g/kg/day.[20,21] However, some adverse reactions are reported. Hypersensitivity with different doses was observed in a few cases. Intravenous administration of high-dose Vitamin C in patients with a history of G6PD deficiency led to hemolytic anemia.[22] Clinical trials on high-dose Vitamin C have reported no major side effects.[1,14,15] Based on the evidence, nephrolithiasis and oxaluria are no longer concerning adverse events. After correct urine sampling, maintaining the urine pH under 2 and temperature under 4°C, <0.5% of the high dose of Vitamin C will be excreted in the form of oxalic acid in the urine.[23]

The primary outcome was a change in the SOFA score. In this scoring system, each of five parameters represents the specific organ function, Glasgow Coma Scale for the mental state, platelets for bone marrow state, PF ratio for the lung injury, mean arterial pressure for the cardiovascular state, and creatinine for renal function. Hence, the SOFA score was considered the primary outcome to assess overall body function.

The secondary outcomes included the level of National Early Warning Score (NEWS) 2, Ordinal Scale for Clinical Improvement, CRP, ferritin, and neutrophil-to-lymphocyte ratio (NLR), length of hospital stays, need for intensive care unit (ICU) admission, and mortality.

NEWS2 consists of six vital signs and can predict the risk of disease worsening in the early stages.[24] Ordinal Scale for Clinical Improvement is recommended by the WHO as a clinical scale of choice during the COVID-19 pandemic, and to make the results of clinical trials comparable.[25] Therefore, these two indices were measured to evaluate clinical conditions. CRP, ferritin, and NLR were the main plasma markers of the cytokine storm. NLR was calculated by dividing neutrophil counts over lymphocyte counts in the complete blood count with a differentiation test on the specified day. Length of hospital stays and need for ICU admission after enrollment were recorded until discharge or expiration. In the case of discharge, survival follow-up was performed by a telephone call on day 28 of enrollment.

According to the Kidney Disease: Improving Global Outcomes Clinical Practice Guideline,[26] acute kidney injury (AKI) is defined as an increase in serum creatinine (SCr) by 0.3 mg/dl within 2 days, or an increase in SCr to 1.5 times baseline, which is presumed to have happened within the prior 1 week, or urine volume 0.5 ml/kg/h for 6 h. The occurrence of AKI was recorded during hospitalization after enrollment.

The sample size was calculated based on Vitamin C supplementation effect on the primary outcome (SOFA score), equal to a 4.3 score reduction in comparison with a 0.3 score increase in the placebo group in another trial.[14] Therefore, to have an 80% power to see such an effect at an alpha of 5% and a withdrawal rate of 20%, 35 patients would have to be randomized in each group.

Patients were visited every day until discharge or expiration by the investigators. Oxygen saturation at rest, oxygen supplementation device, respiratory rate, temperature, heart rate, and blood pressure were recorded every day. NEWS2 score, Ordinal Scale for Clinical Improvement, and SOFA score were calculated on days 0, 3, and 5. Ferritins, CRP, and complete blood count with differentiation test were also requested on these days.

The *t*-test/Mann–Whitney *U*-test was applied to compare the numerical variables described as the mean with standard deviation or median with interquartile range according to distribution. The Chi-square and Fisher's exact test were used to compare the categorical data represented as frequencies and proportions.

Variables are shown over time in line plots and compared and evaluated between groups with a mixed-effect generalized linear model with Gaussian distribution, considering the group of randomization, an interaction between time group as fixed effects, patients as a random effect to account for repeated measurements, and the time of measurement (as a continuous variable). The 28-day mortality was estimated by Kaplan–Meier analysis to reflect the early survival differences between the two groups. All statistical analyses were done by

STATA (StataCorp. 2015. Stata Statistical Software: Release 14. College Station, TX: StataCorp LP.), and $P < 0.05$ was considered statistical significance.

Results

Ninety of the 187 patients who were assessed for eligibility, between April and November 2020, Underwent randomization. The flow diagram of patient enrollment, randomization, and analysis is presented in Figure 1. Eighty-nine patients were excluded as they did not meet the criteria (primarily participation in other trials), and eight were excluded for disagreement with participation. Ninety patients were randomized blindly into two groups (HDIVC and placebo). Six patients were discharged during the treatment in the HDIVC group, and one patient expired before receiving the second dose. In the placebo group, seven patients were discharged before the 2nd day of treatment. Hence, these patients did not have comparative data and were excluded from primary outcome analysis, but they were included in the mortality prediction model. Two patients in the Vitamin C group could not complete 4 days of study; one showed adverse allergic reactions, and the other declined to cooperate with the trial. Finally, the data of 37 patients in each group were analyzed for the effect of treatment on the primary outcome.

The baseline characteristics are presented in Tables 1a and 1b. The median age of patients was 57.84 ± 14.72 years and 58.89 ± 14.46 in the HDIVC arm and the placebo arm, respectively. The treatment group consisted of 59.5% male gender and 54.1% in the control group. Hypertension was the dominant comorbidity in both the arms. Comparing the two groups revealed no difference in baseline parameters at the time of enrollment, except for the number of symptomatic days. Patients in the Vitamin C group had significantly lower days of symptoms ($P = 0.05$).

The level of SOFA score as the primary outcome did not significantly differ between the HDIVC and placebo groups [Table 2a]. However, as shown in Figure 2, more reduction in this score was observed in the treatment group. During the first 3 days, a less increase in SOFA score was observed in the HDIVC arm compared to the placebo arm (+0.026 vs. +0.204). Moreover, from day 3 to day 5, the HDIVC group significantly reduced this score (−0.462 vs. −0.036).

Analysis of secondary outcomes failed to detect significant differences between the two groups. Treatment with HDIVC had no effect on NEWS score, Ordinal Scale for Clinical Improvement, SF ratio, CRP,

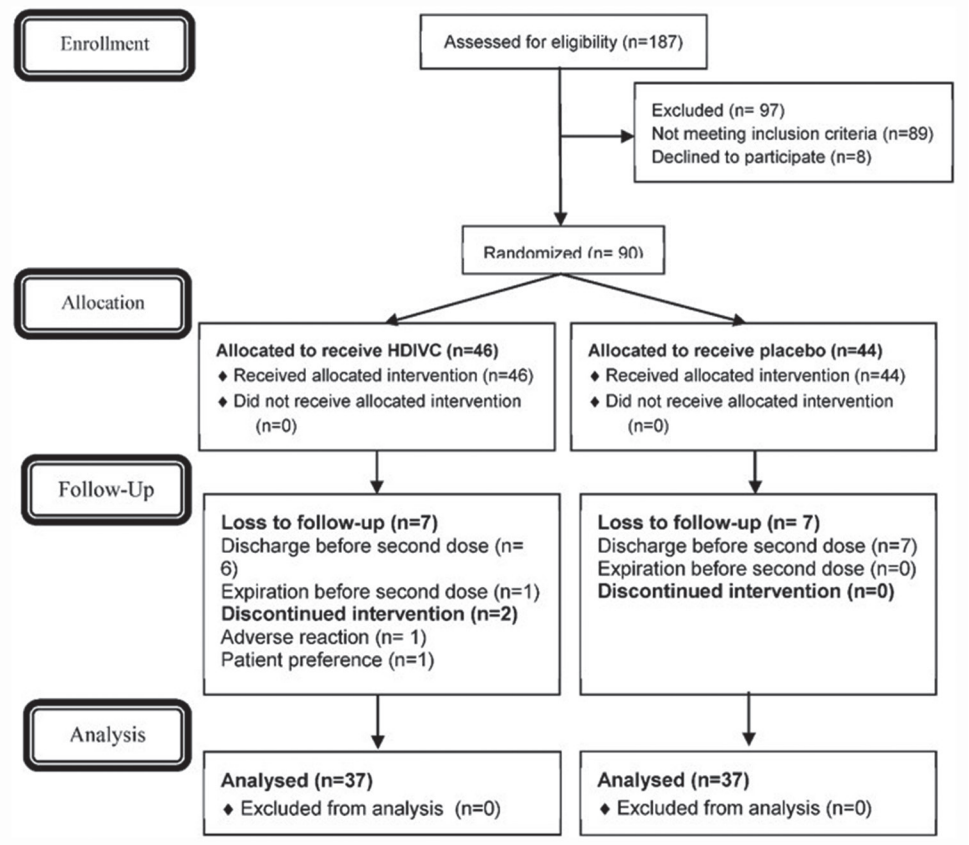

Figure 1: Flow diagram of patients. HDIVC: High-dose intravenous Vitamin C

ferritin, and NLR levels. The statistical comparison of data is presented in Tables 2a and 2b. Figure 3 also shows the changes in these indices in two groups.

According to the analysis [Table 2b], treatment with HDIVC could not reduce the number of hospitalization or ICU admission days (P = 0.517 and 0.718, respectively).

At the end of hospitalization, death occurs in six (18%) patients of the placebo group and in four (14%) patients of the treatment group. Kaplan–Meier analysis was used to assess the 28-day mortality and survival curves and showed no differences between the two treatment arms [P = 0.953, Figure 4].

Treatment with corticosteroids or antiviral agents was not different between the two groups [Table 1b]. In the placebo group, 25% of patients, and in the

Table 1a: Baseline demographic data of patients in Vitamin C and placebo groups

Variable	High-dose Vitamin C group (n=37)	Placebo group (n=37)	P
Demographics			
Age (years)	57.84±14.722	58.89±14.460	0.757
Weight (kg)	79.57±16.431	75.59±13.488	0.259
Gender			
Male	22 (59.5)	20 (54.1)	-
Female	15 (40.5)	17 (45.9)	
Comorbidity			0.792
Diabetes	5 (13.5)	7 (18.9)	
IHD	8 (21.6)	6 (16.2)	
HTN	5 (13.5)	5 (13.5)	
Obesity	1 (2.7)	1 (2.7)	
No comorbidity	10 (27.0)	10 (27)	
Symptoms at enrollment			0.645
Dyspnea	11 (29.7)	10 (27)	
Fever	11 (29.7)	15 (40.5)	
Asthenia	4 (10.8)	4 (10.8)	
Need for intubation	5 (13.5)	5 (13.5)	1
Need for NIV	8 (21.6)	11 (29.7)	0.298

*Data are presented as mean±SD, n (%), or median (IQR). IHD: Ischemic heart disease, HTN: Hypertension, SD: Standard deviation, IQR: Interquartile range, NIV: Noninvasive ventilation

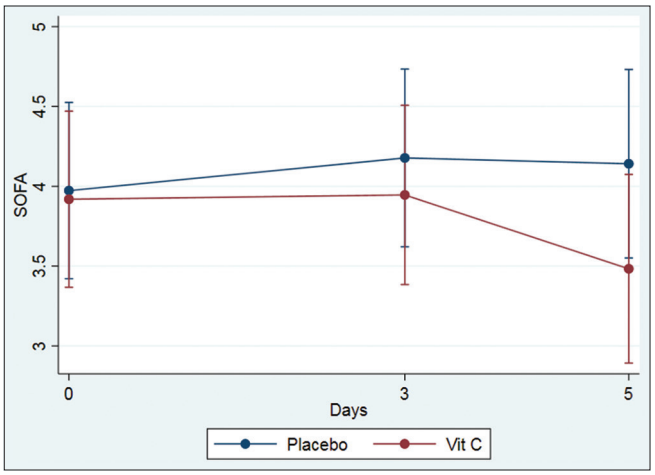

Figure 2: Effect of treatment on SOFA score on days 0, 3, and 5. There was no significant change between treatment arms on days 0, 3, and 5. Differences between days show less increase on day 3 (+0.026 vs. +0.204) and more reduction on day 5 (−0.462 vs. −0.036). SOFA: Sequential Organ Failure Assessment

Table 1b: Baseline scores and measured parameters of patients in Vitamin C and placebo groups

Variable	High-dose Vitamin C group (n=37)	Placebo group (n=37)	P
Assessed scores and measured parameters			
SOFA score	2.89±1.329	3.05±1.373	0.607
SF ratio	211.11 (97.89-254.51)	211.11 (99.47-246.86)	1
PF ratio	157.77 (71.05-206.64)	148.88 (74.73-199.72)	0.816
NEWS score	6.24±2.640	6.11±2.157	0.823
Ordinal Scale for Clinical Improvement	4.41±0.498	4.38±0.545	0.824
GCS	14.57±1.04	14.86±0.48	0.121
Platelet (cells×10^3/ml^3)	227 (178.5-283)	227 (179-282.5)	0.774
MAP (mmHg)	86.5 (81.65-93.30)	93.00 (83.30-98.30)	0.117
Creatinine (mg/dL)	1.00±0.232	1.12±0.311	0.07
GFR (mL/min)	82.50 (66.32-109.96)	69.81 (52.86-95.30)	0.07
Total bilirubin (mg/dL)	1.02±0.495	0.99±0.423	0.808
CRP (mg/L)	62.00 (18.50-79.50)	66.50 (47.50-80.75)	0.415
NLR	7.28 (3.09-12.04)	8.15 (4.02-16.3)	0.622
Ferritin (ng/mL)	509.00 (277.00-853.00)	593.50 (291.00-1078.50)	0.891
Consumption antiviral	9 (25)	13 (35.1)	0.446
Consumption corticosteroid	23 (62.2)	20 (54.1)	0.638

*Data are presented as mean±SD, n (%) or median (IQR). SOFA: Sequential Organ Failure Assessment, NEWS: National Early Warning Score, SF ratio: SpO2/FiO2 ratio, PF ratio: PaO2/FiO2 ratio, CRP: C-reactive protein, NLR: Neutrophil-to-lymphocyte ratio, GCS: Glasgow Coma Scale, MAP: Mean arterial pressure, GFR: Glomerular filtration rate, SD: Standard deviation, IQR: Interquartile range

Table 2a: Scoring indices assessed during treatment

	High dose Vitamin C	Placebo	Difference	95% CI	*P*
SOFA score					
At baseline	3.92±0.28	3.97±0.28	−0.05	−0.83-0.72	0.89
At day 3	3.94±0.29	4.18±0.28	−0.23	−1.02-0.56	0.57
At day 5	3.48±0.30	4.14±0.30	−0.66	−1.49-0.18	0.12
NEWS score					
At baseline	6.24±0.43	6.11±0.43	0.13	−1.05-1.32	0.82
At day 3	6.02±0.43	5.20±0.43	0.82	−0.38-2.01	0.18
At day 5	5.51±0.46	5.04±0.46	0.47	−0.80-1.75	0.47
Ordinal Scale for Clinical Improvement					
At baseline	4.41±0.16	4.38±0.16	0.03	−0.42-0.47	0.90
At day 3	4.38±0.16	4.24±0.16	0.14	−0.31-0.58	0.55
At day 5	4.03±0.16	3.81±0.16	0.22	−0.23-0.66	0.34

*Data are presented as mean±SD, n (%), or median (IQR). SOFA score is considered as primary outcome. SOFA: Sequential Organ Failure Assessment, NEWS: National early warning score, CI: Confidence interval, SD: Standard deviation, IQR: Interquartile range

Table 2b: Other secondary outcomes assessed during treatment

	High dose Vitamin C	Placebo	Difference	95% CI	*P*
SF ratio					
At baseline	205.61±18.64	193.63±18.64	11.98	−39.69-63.65	0.65
At day 3	202.76±18.85	212.48±18.74	−9.72	−61.82-42.37	0.71
At day 5	213.25±19.48	226.71±19.46	−13.46	−67.42-40.50	0.62
CRP					
At baseline	53.32±6.00	63.92±6.09	−10.59	−27.36-6.17	0.22
At day 3	45.78±7.02	51.44±7.28	−5.66	−25.49-14.18	0.58
At day 5	35.29±6.91	35.84±7.42	−0.55	−20.43-19.33	0.98
Ferritin					
At baseline	724.29±149.40	918.86±145.01	−194.57	−602.65-213.50	0.35
At day 3	656.76±180.28	1183.33±167.01	−526.56	−1008.21-−44.91	0.032
At day 5	808.69±189.88	835.59±166.23	−26.90	−521.51-467.71	0.91
NLR					
At baseline	9.42±1.45	9.69±1.47	−0.26	−4.32-3.79	0.90
At day 3	9.87±1.48	9.56±1.47	0.32	−3.77-4.41	0.88
At day 5	10.07±1.58	10.96±1.52	−0.89	−5.19-3.41	0.68
Hospitalization days after enrollment	9.24±7.50	8.19±5.34	−1.05	−4.29-2.18	0.52
ICU-admission days	1.95±5.89	1.51±4.25	0.44	−2.81-1.95	0.72

*Data are presented as mean±SD, *n* (%), or median (IQR). SF ratio: SpO2/FiO2 ratio, CRP: C-reactive protein, NLR: Neutrophil-to-lymphocyte ratio, ICU: Intensive care unit, CI: Confidence interval, SD: Standard deviation, IQR: Interquartile range

Vitamin C group, 35% of patients received antiviral agents (P = 0.446). Treatment with corticosteroids was administered in 62.2% of patients in the placebo arm and 54.1% in the Vitamin C arm (P = 0.638).

No major adverse events, including nephrolithiasis, anaphylaxis, and hemolytic anemia, were observed during the study. One patient experienced an allergic reaction in the Vitamin C group during infusion and was excluded from the study. Allergic reactions in the form of breathing difficulty and flushing happened during sleep after 6 h of first-dose infusion and resolved after infusion discontinuation. Two of our patients had a history of nephrolithiasis. However, no sign of disease activation was observed during the treatment or hospitalization.

Considering the level of creatinine and GFR at the time of enrollment, baseline renal function was equal between the two groups. However, the incidence of AKI during hospitalization was lower in the Vitamin C group (27% in the placebo arm vs. 10.8% in the HDIVC arm). Still, this difference did not reach the level of significance (P = 0.068).

Discussion

This double-blind, randomized, placebo-controlled trial in patients with moderate-to-severe disease of COVID-19 identified no significant difference in the improvement of SOFA with an early administration of HDIVC. However, the signal of probable effectiveness due to reduced SOFA score in the Vitamin C group was detected.

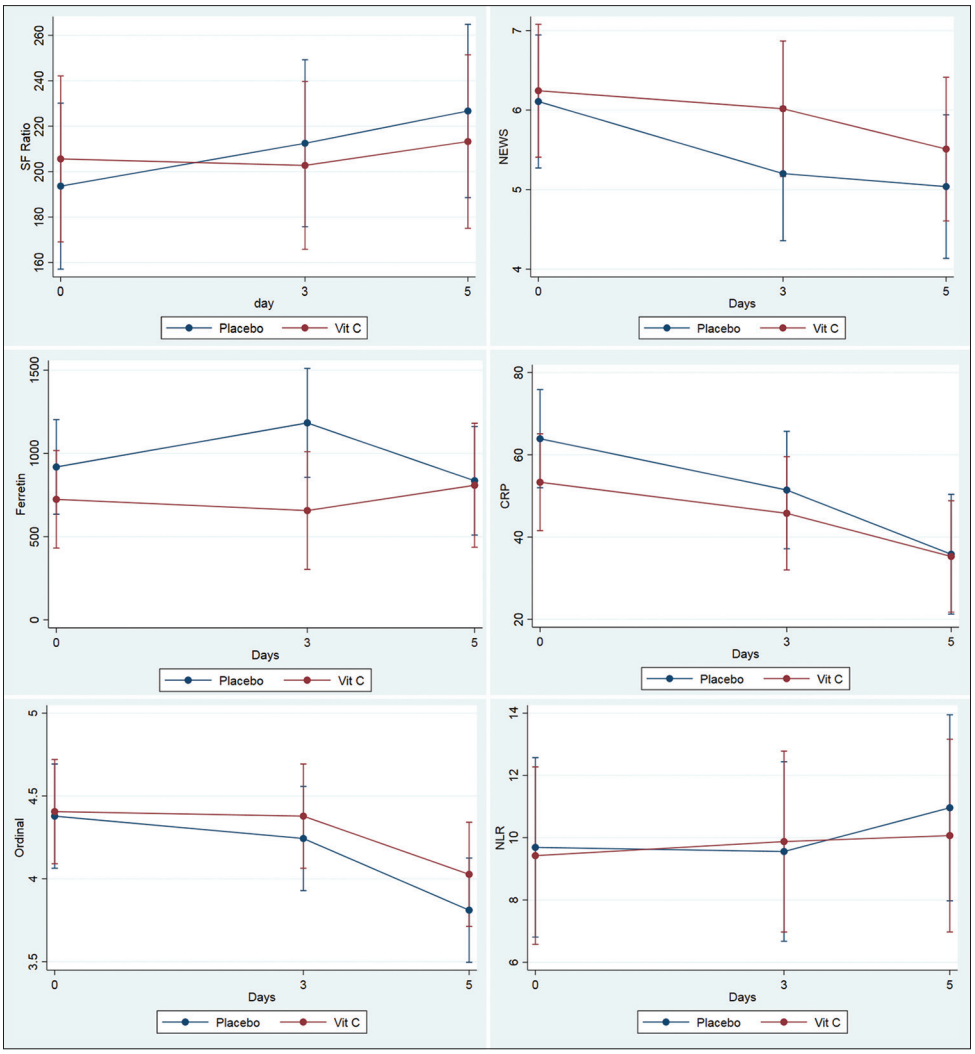

Figure 3: Changes in SF ratio, NEWS score, Ordinal Scale for Clinical Improvement, ferritin, CRP, and NLR during the treatment by Vitamin C or placebo. None of the variations in these parameters have reached statistical significance. SF ratio: SpO2/FiO2 ratio, NEWS score: National Early Warning Score, CRP: C-reactive protein, NLR: Neutrophil/lymphocyte ratio

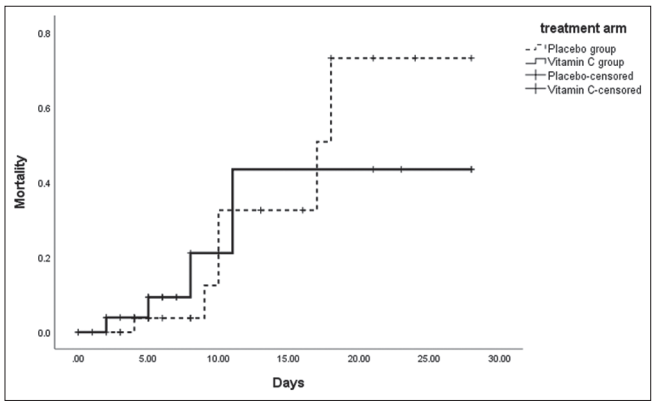

Figure 4: The 28-day mortality from randomization (day 0) to day 28 among patients is based on types of treatment

Previously, it showed that Vitamin C is beneficial in preventing endothelial damage, inhibiting neutrophil apoptosis, and oxidative injury. Current data on the beneficial effects of HDIVC are inconclusive.[7,8,27] Prior clinical data regarding the safety and efficacy of using high-dose Vitamin C for severe sepsis suggested that early and aggressive repletion of Vitamin C would benefit organ dysfunction. Fowler *et al*.[14] found significant improvement in SOFA score by administering Vitamin C in the early stages of sepsis, However, administration of the same dose in later stages of disease in CITRIS-ALI did not support this finding.[15,28] These findings support the assumption that treatment with Vitamin C after ARDS development could not affect clinical outcomes. In one randomized controlled trial on 24 g/day Vitamin C in critically ill COVID-19 patients, signs of improvement were observed despite insignificant changes in SOFA score. Although this study aimed to enroll critical patients, the lowest SpO2 of patients was 93%, and thus, ARDS had not been developed at the time of trial conduction.[1]

Besides, in our study, analysis of secondary outcomes revealed no significant beneficial effects of treatment.

Treatment with HDIVC did not affect hospitalization or ICU-free days. Furthermore, the mortality rate on day 28 was the same between the study arms. In contrast to our results, Fowler *et al*. administered daily doses of 200 mg/kg of Vitamin C for 4 days to critically ill patients with severe sepsis and observed a significant reduction in 28-day mortality and an increase in ICU-free and hospital-free days.[15] Lv *et al*. administered approximately half-dose used by Fowler to septic patients during ICU stay and observed significantly lower mortality rates.[7] A meta-analysis on the effect of using different doses of Vitamin C in critically ill adult patients showed that 3–10 g/day doses of Vitamin C are associated with reduced mortality rates in patients.[29] In another study, although administering 60 mg/kg/day of Vitamin C for 96 h to critically ill patients with severe pneumonia was associated with improving CRP, SOFA score, and PF ratio, the mortality rate was not improved.[30] Data regarding the effect of Vitamin C on the clinical outcomes of COVID-19 patients are contradictory. In critically ill COVID-19 patients, Gao *et al*. observed remarkable improvement in 28-day mortality by administering 6-g Vitamin C IV daily for 4 days.[31] In contrast, no mortality benefit was observed by Zhang *et al*. after administration of 24 g/day of Vitamin C for the same duration of treatment.[1]

To classify the severity of the disease, the NEWS2 score was used beside the SOFA score in our study. NEWS2 score improved in both the study arms without any significant difference. We also did not see any substantial change in improving CRP, ferritin, and NLR along with other previous studies during the treatment.[15]

Similar to our results, early administration of 8 g/day of oral Vitamin C for 10 days in outpatients with confirmed SARS-CoV-2 infection showed no improvement in symptoms duration and mortality.[17] However, the plasma level of Vitamin C was not measured in this study, and based on pharmacokinetic studies,[32,33] the therapeutic plasma level of Vitamin C (175 mg/mL or 1000 mmol/L) can be achieved by intravenous administration of at least 10-g Vitamin C. The oral route has saturable absorption, and doses of more than 500 mg will be partially absorbed,[32,34] so achieving the therapeutic level of Vitamin C in this study is uncertain.

Together, these findings revealed that treatment with intravenous high-dose Vitamin C in the early stages of infection with SARS-CoV-2 does not affect clinical and biological endpoints or disease progression, albeit it showed some potential in preventing organ dysfunction.

Our study has several limitations. The treatment efficacy could be undetectable due to this study's limited number of patients. Days of symptoms at enrollment between the two groups showed statistically significant differences ($P = 0.05$); this can lead to defacement of results, but disease severity in all patients was not critical, and the aim of our study was the prevention of disease progression to a critical state.

Vitamin C plasma level of more than 175 mg/L is supposed to be therapeutic and scavenge the whole plasma's free radicals.[33] However, in this study, we used a fixed dose of Vitamin C (12 g/day), which could establish different plasma levels in each patient. At the same time, we did not measure plasma levels of Vitamin C, and reaching pharmacologic plasma levels was uncertain. Furthermore, pharmacokinetic studies on Vitamin C showed hypovitaminosis after 48 h of treatment discontinuation,[33] so the suitable duration of therapy is still unknown. The Shanghai Expert Group also suggests the continuation of treatment for up to 10 days.[35] Thus, it is recommended that a longer duration of therapy could be beneficial.

Although other treatments were recorded during the study and analysis showed no difference between the two groups, the effect of each antiviral agent or amount of corticosteroid received by inpatients was not considered in this assessment.

In conclusion, treatment of patients with moderate-to-severe COVID-19 with 12 g/d Vitamin C for 4 days did not improve any clinical or biological parameters and also could not reduce the mortality rate at day 28.

Authors' Contribution

Z. Labbani-Motlagh, R. Aliannejad, A. Sadeghi, M. Jafary, and M. Talaschian: Acquisition of clinical data and patient's diagnosis and treatment, interpretation of data, drafting the article, and final approval of the article.

G. Shafiee and R. Heshmat: Acquisition of data, the conception and design of the study, analysis and interpretation of data, drafting the article, and final approval of the article.

S. Amini, M. Akhtari, A. Jamshidi, M. Mahmoudi, and K. Sadeghi: The conception and design of the study, interpretation of data, revising the article critically for important intellectual content, and final approval of the article.

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Conflicts of interest

There are no conflicts of interest.

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