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Original Research

The effect of High-Dose Vitamin C Treatment for Acute Respiratory Failure Due to Coronavirus Disease Pneumonia on Mortality and Length of Intensive Care Stay: A Retrospective Cohort Study

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Abstract

Objectives: In our study, we aimed to determine the effect of vitamin C on short-term mortality and length of intensive care unit (ICU) stay in patients with coronavirus disease (COVID-19) followed up in the ICU.

Methods: The patients who received and those who did not receive the high-dose intravenous vitamin C protocol were assigned to the treatment and control groups, respectively. The primary study findings in both groups were length of ICU stay and short-term mortality, while the secondary findings were vasopressor and invasive mechanical ventilation requirements and change in sequential organ failure assessment score from the 0 to the 96th hour.

Results: Thirty-eight patients were included in the treatment group and 40 were included in the control group. The mortality rates were 44% and 60% in the treatment and control groups, respectively; however, the difference between the groups was not statistically significant (p>0.05). The median length of ICU stay in both groups was 10 days (p>0.05). No significant differences in the invasive mechanical ventilation and vasopressor requirements were found between the groups (p>0.05).

Conclusion: Consequently, the high-dose vitamin C therapy in the patients with acute respiratory failure due to COVID-19 pneumonia did not reduce the length of ICU stay, mortality, and invasive mechanical ventilation and vasopressor reqirements.

Keywords: Ascorbic acid, coronavirus disease, intensive care, respiratory distress syndrome, sepsis

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Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) causes tissue damage in the endothelium and epithelium, increasing vascular permeability and the risk of lung edema. The expressions of interleukin (IL) 6, IL-2, IL-7, IL-10, interferon gamma, and tumor necrosis factor α are thought to induce an interstitial fibrosis in the lung by causing an abnormal increase (cytokine storm) in plasma levels.[1-3] When these pathogenic factors are taken into account, a table with high mortality from acute respiratory failure and severe acute respiratory distress syndrome (ARDS) emerges in patients with coronavirus disease (COVID-19) followed up in the intensive care unit (ICU). The low

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level of evidence of the recommendations presented in the guidelines, both on the treatment and mechanical ventilation, has brought supportive treatments to the agenda.[4] Recently, many articles have been published on the potential effects of anti-inflammatory and antioxidant treatments such as high-dose vitamin C, vitamin D, zinc, and ozone therapies.[5-7] The fact that high-dose intravenous vitamin C (HDVC) treatment is cheap and easily accessible and reduced mortality in patients with sepsis and ARDS the in previous studies suggests that it may also be beneficial for patients with COVID-19.[8,9] In this study, we aimed to determine the effect of vitamin C on the short-term mortality and length of ICU stay of patients with COVID-19.

Methods

We conducted a retrospective cohort study using data recorded in the data system of five COVID-19 cohort ICUs in our hospital. Our study was started after obtaining approval from the general ethics committee of our hospital (approval No. 3021) and registration at ClinicalTrials.gov (NCT04710329). The study was performed in accordance with the Declaration of Helsinki.

All the data of the patients aged >18 years who were admitted to the ICU due to acute respiratory failure due to COVID-19 pneumonia between March 2020 and June 2020 were reviewed. Our study included patients whose COVID-19 diagnosis was confirmed with a reverse transcriptase-polymerase chain reaction test and pneumonia was diagnosed on the basis of clinical and radiological findings, and who developed acute respiratory failure (PaO_2/FiO_2 < 300 despite the use of a 6–l/min reservoir mask) due to pneumonia.

Patients with active kidney stones, hepatic insufficiency, renal failure, end-stage cancer, and primary lung pathology other than pneumonia (lung cancer and cardiopulmonary edema) or who were receiving anti-cytokine therapy (tocilizumab and anakinra) were not included in the study. Patients with diabetic ketoacidosis or hyperglycemia requiring >6 blood sugar measurements in 24 h and patients with <96 h of ICU stay were excluded from the study.

Patients who were admitted to the ICU between May and July 2020 and received the HDCV protocol formed the treatment group (Vitamin C group). In the first period of the pandemic, patients who were admitted to the ICU between March and April 2020 but did not receive the HDCV protocol formed the control group (non-Vitamin C group).

The primary study findings consisted of 28–day mortality and length of ICU stay for the patients in both groups, while the secondary findings were vasopressor need, invasive mechanical ventilation requirement, and changes in the Sequential organ failure assessment (SOFA) score at the 0–96th h.

The treatment protocol consisted of an intravenous administration of 6 g of vitamin C daily in 4 equal doses every 6 h, for a total of 96 h. Vials containing 1.5 g of vitamin C were placed in 100–cc 5% dextrose and infused intravenously in 30–60 min. Prepared serum bottles and sets were wrapped with aluminum foil to protect them from sunlight.

The Ministry of Health COVID-19 Treatment Guidelines and international guidelines were based on the selection of respiratory support, mechanical ventilation management, fluid resuscitation, antiviral agent treatments, and vasopressor administirations.[4,10,11]

Patient data were obtained from the patient information system of our hospital and nurse observation forms. Age, sex, body mass index (BMI), comorbidities (coronary artery disease, hypertension, diabetes mellitus, chronic obstructive pulmonary disease, etc.), and PaO_2/FiO_2 ratios were recorded at admission to the ICU for all the patients. Blood lactate levels and SOFA scores were recorded at the beginning and 96th h, and ferritin, C-reactive protein (CRP), and procalcitonin values were recorded at the beginning, 48th h, and 96th h. The short-term mortalities, lengths of ICU stay, vasopressor needs, and invasive mechanical ventilation requirements of the patients were recorded. Short-term mortality was defined as death up to 28 days.

Statistical Reviews

For the statistical analyses, the number cruncher statistical system 2007 program (Kaysville, Utah, USA) was used. While evaluating the study data, alongside the descriptive statistical methods (average, standard deviation, median, frequency, ratio, minimum, and maximum), in the comparison of the quantitative data, the Student t-test was used for comparing normally distributed variables in the two groups and the Mann–Whitney U-test was used for two-group comparisons of variables with abnormal distributions. The Wilcoxon signed-rank test was used for in-group evaluations. The Pearson Chi-square and Fisher exact tests were used to compare qualitative data. Significance was evaluated at p=0.05.

Results

Between March 2020 and June 2020, the data of 170 patients aged >18 years who were admitted to the COVID-19 ICU under the diagnosis of acute respiratory failure due to COVID-19 pneumonia were collected. Two patients with active kidney stones, one patient with hepatic insufficiency, 12 patients with active renal failure, six patients with terminal-stage malignancy, four patients with

lung cancer, and two patients with decompensated left heart failure were not included in the study. The reason for the exclusion was diabetic ketoacidosis in one patient, uncontrolled hyperglycemia in six patients, tocilizumab treatment in two patients, and <96 h of ICU stay in 56 patients. We included in our study 78 patients who met the inclusion criteria (Fig. 1). Thirty-eight patients constituted the vitamin C group; and 40 patients, the non-vitamin C group. No statistically significant differences in age, sex, BMI, and comorbidities were found between the groups (p>0.05; Table 1).

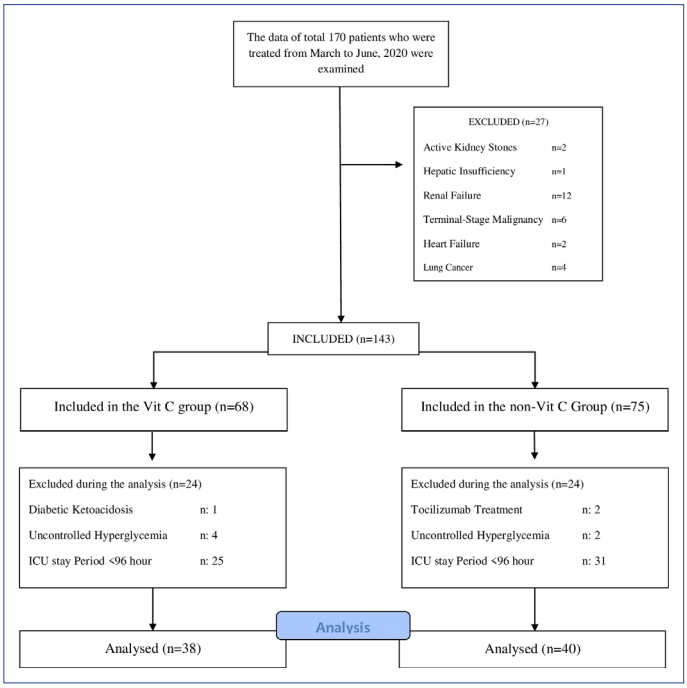

Figure 1. Flow diagram.

Initially, no significant differences in mean PaO_2/FiO_2 ratio, SOFA score, and lactate, ferritin, CRP, and PCT values were found (p>0.05). At the 96th h, the mean SOFA scores were 5.3 and 7.4, the mean CRP levels were 171.9 and 205.4 mg/dL, and the mean PCT levels were 4 and 4.7 ng/m in the vitamin C and non-vitamin C groups, respectively. All the differences were statistically significant (p=0.005, p=0.043, and p=0.021, respectively; Table 2).

We found no significant differences in the median SOFA score and ferritin, CRP, lactate, and PCT levels at the beginning and 96th h (p>0.05). However, while the initial median PaO_2/FiO_2 ratio was 125, it statistically significantly increased to 153 at the 96th h (p=0.005). In the non-vitamin C group, no significant differences in the median PaO_2/FiO_2, lactate level, and CRP level were found between the beginning and 96th h (p>0.05). In the non-vitamin C group, the median SOFA score was 4 at the beginning and 7.5 at the 96th h, the ferritin level increased from 553 to 999 ug/L, and the PCT level increased from 0.5 to 1.4 ng/m. All the differences were statistically significant (p=0.001, p=0.001, and p=0.001, respectively; Table 3).

No statistically significant differences in median lactate and PaO_2/FiO_2 values were found between the 0 and 96th h changes in both groups (p>0.05). The median SOFA score increased from 4 to 5 in the vitamin C group and from 4 to 7.5 in the non-vitamin C group. The difference between the changes was statistically significant (p=0.008). The median ferritin value decreased from 665 to 620 ug/L in the vitamin C group and increased from 553 to 999 ug/L in the non-vitamin C group, and the difference between the changes was statistically significant (p=0.004). The median CRP level decreased from 186 to 145 mg/dl in the vitamin C group

Table 1. Patients' demographics and comorbidities

	Vitamin C Group (n=38)	Non-vitamin C Group (n=40)	p
Age (year)			
Mean±SD	68.03±13.35	66.70±12.73	[a]0.655
Sex			
Female	8 (21.1)	13 (32.5)	[b]0.255
Male	30 (78.9)	27 (67.5)	
BMI (kg/m^2)			
Mean±SD	25.80±3.26	26.65±2.40	[a]0.189
Comorbidity			
Diabetes mellitus	14 (36.8)	15 (37.5)	[b]0.952
Hypertension	17 (44.7)	17 (42.5)	[b]0.842
Coronary artery disease	9 (23.7)	9 (22.5)	[b]0.901
Chronic obstructive pulmonary disease	5 (13.2)	5 (12.5)	[b]0.931
Other	14 (36.8)	14 (35.0)	[c]1.000

[a]Student-t test; [b]Pearson Chi-square test; [c]Fisher's exact test; BMI: Body mass index.

Table 2. Comparison of PaO2/FiO2, SOFA, Lactate, Ferritin, CRP, and PCT values of the groups at the baseline and at the 96th h

	Baseline			96th h		
	Vitamin C Group(n=38)	Non-Vitamin C Group(n=40)	p	Vitamin C Group(n=38)	Non-Vitamin C Group(n=40)	p
PaO_2/FiO_2						
Mean±SD	146.6±50.9	145.1±52.5	[c]0.964	177.9±84.2	191±183.4	[c]0.159
Median (IQR)	125 (110–160)	129 (110.5–160)		153.3 (115–200)	130.5 (100–225)	
SOFA						
Mean±SD	4.7±2.7	4.9±1.6	[c]0.355	5.3±3.2	7.4±3.2	[c]0.005**
Median (IQR)	4(3–6)	4 (4–7)		5 (3–7)	7.5 (4.5–10)	
Lactate (mmol/L)						
Mean±SD	1.7±0.9	1.7±0.8	[c]0.928	1.8±0.9	1.9±1.1	[c]0.818
Median (IQR)	1.4(1.2–2)	1.4 (1.2–1.8)		1.7 (1.3–2)	1.5 (1.3–2.2)	
Ferritin (ug/L)						
Mean±SD	822.4±703.3	850.7±1398.6	[c]0.631	934.1±1131.2	1364.6±1681.6	[c]0.079
Median (IQR)	665(321–1176)	553(290.5–944)		620 (234–1038)	999.5 (480.5–1451.5)	
CRP (mg/dL)						
Mean±SD	204.9±85.8	194.7±118	[c]0.562	171.9±138.1	205.4±102	[c]0.043*
Median (IQR)	186 (150–240)	195.5 (116.5–235)		145 (74.1–214)	174.5(133.5–276)	
PCT (ng/m)						
Mean±SD	2.1±5.5	2.4±8.1	[c]0.984	4.1±16.2	4.7±7.3	[c]0.021*
Median (IQR)	0.4 (0.2–1.1)	0.5 (0.2–1.3)		0.5(0.2–1.5)	1.4(0.4–4.9)	

[c]Mann whitney U test, *p<0.05 **p<0.01 CRP=C-reactive protein, PCT=Procalcitonin, SOFA=Sequential organ failure assessment, mg/dL=milligram/deciliter, mmol/L= millimole/liter, ug/L= microgram/liter, ng/m=nanogram/milliliter.

and from 195 to 174 mg/dL in the non-vitamin C group, and the differences were statistically significant (p=0.048). The median PCT level increased from 0.4 to 0.5 ng/m in the vitamin C group and from 0.5 to 1.4 ng/m in non-vitamin C group, indicating statistically significant changes (p=0.006 for both groups; Table 4).

No significant differences were found between the groups in terms of length of ICU stay, mortality rate, invasive mechanical requirement, and vasopressor need (p>0.05; Table 5).

Table 3. Comparison of group's self, baseline and 96th h PaO_2/FiO_2, Lactate, SOFA, Ferritin, CRP and PCT values

	Vitamin C Group (n=38)			Non-Vitamin C Group (n=40)		
	Baseline	96th h	p	Baseline	96th h	p
PaO_2/FiO_2						
Median (IQR)	125 (110–160)	153.3 (115–200)	0.005**	129 (110.5–160)	130.5 (100–225)	0.347
SOFA						
Median (IQR)	4 (3–6)	5 (3–7)	0.131	4 (4–7)	7.5 (4.5–10)	0.001**
Lactate (mmol/L)						
Median (IQR)	1.4 (1.2–2)	1.7 (1.3–2)	0.805	1.4 (1.2–1.8)	1.5 (1.3–2.2)	0.264
Ferritin(ug/L)						
Median (IQR)	665 (321–1176)	620 (234–1038)	0.451	553 (290.5–944)	999.5 (480.5–1451.5)	0.001**
CRP(mg/dL)						
Median (IQR)	186 (150–240)	145 (74.1–214)	0.060	195.5 (116.5–235)	174.5 (133.5–276)	0.609
PCT(ng/m)						
Median (IQR)	0.4 (0.2–1.1)	0.5 (0.2–1.5)	0.958	0.5 (0.2–1.3)	1.4 (0.4–4.9)	0.001**

Wilcoxon signed rank test, *p<0.05, **p<0.01, CRP=C-reaktif protein, PCT=Procalcitonin, SOFA=Sequential organ failure assessment, mg/dL=milligram/deciliter, mmol/L=millimole/liter, ug/L=microgram/liter, ng/m=nanogram/milliliter.

Table 4. 0–96th h changes in PaO_2/FiO_2, Lactate, SOFA, Ferritin, CRP and PCT values' between groups

	Vitamin C Group (n=38)	Non-Vitamin C Group (n=40)	p
PaO_2/FiO_2			
Median (IQR)	−19.9 (−70/4)	−8 (−70.3/54)	[c]0.280
SOFA			
Median (IQR)	0 (−2/0)	−2.5 (−5/0)	[c]0.008**
Lactate(mmol/L)			
Median (IQR)	0.1 (−0.9/0.5)	−0.1 (−0.6/0.2)	[c]0.596
Ferritin(ug/L)			
Median (IQR)	38.5 (−166/291)	−216.5 (−706.5/9)	[c]0.004**
CRP (mg/dl)			
Median (IQR)	28.5 (−27/107)	−3 (−82.5/62)	[c]0.048*
PCT(ng/m)			
Median (IQR)	0 (−0.4/0.3)	−0.5 (−2.4/0)	[c]0.006**

[c]Mann whitney U test, *p<0.05 **p<0.01 CRP=C-reactive protein, PCT=Procalcitonin, SOFA=Sequential organ failure assessment, mg/dL=milligram/deciliter, mmol/L=millimole/liter, ug/L= microgram/liter, ng/m=nanogram/milliliter.

Table 5. Comparison of mortality, Length of ICU stay, IMV Requirements and vasopressor need of groups

	Vitamin C Group (n=38)	Non-Vitamin C Group (n=40)	p
Length of ICU Stay			
Median(IQR)	10 (7–16)	10 (7–14.7)	[c]0.729
Mortality	17 (44.7)	24 (60.0)	[b]0.177
IMV Requirement	28 (73.7)	30 (75.0)	[b]0.894
Vasopressor Need	13 (34.2)	22 (55.0)	[b]0.065

[c]Mann–Whitney U-test, [b]Pearson Chi-square test, IMV=Invasive mechanical ventilation, ICU=Intensive care unit.

Discussion

In this study, in the critically ill patients with COVID-19 diagnosis who were followed up in the ICU, HDVC treatment did not reduce the short-term mortality, length of ICU stay, and need for invasive mechanical ventilation and vasopressor. However, it had positive effects on the SOFA score changes from the 0 to the 96th h.

Vitamin C has an indirect antiviral activity and has been shown to be effective not only for respiratory viral infections but also for the treatment of viral infections such as varicella-zoster virus, herpes simplex virus, and human immunodeficiency virüs.[12-14] It reduces the production of proinflammatory modulators regulated by nuclear factor kappa-B; thus, this effect can prevent the formation of a cytokine storm. Considering all these effects, vitamin C may be a potential option for pneumonia treatment in COVID-19 patients and the treatment and prevention of COVID-19-induced sepsis and ARDS. Chiscano-Camón et al.[15] measured blood vitamin C levels of 18 ICU patients who developed ARDS due to COVID-19 and showed that these values were below the normal limits in all the patients and even at levels that could not be measured in 17 patients. This observation revealed that vitamin C deficiency can also worsen the course of COVID-19.

Many studies have been published in recent years on the use of vitamin C in patients with ARDS, sepsis, and septic shock who were followed up in the ICU. Mortality and length of ICU stay were the primary findings in most of these studies. In the CITRIS-ALI study, 84 of 167 patients with sepsis and ARDS diagnoses who were followed up in the ICU received HDVC for 96 h, and vitamin C supplementation was found to significantly reduce the length of ICU stay and mortality.[16] In the study by Kim et al.,[17] which is one of the most recent examples of such clinical study, thiamine and hydrocortisone therapies were administered together with HDVC to patients with a diagnosis of severe pneumonia who were followed up in the ICU. They found that the treatment did not reduce the length of ICU stay, and the mortality was 21% in the treatment group and 37% in the control group. Although this difference was not statistically significant, they commented that vitamin C treatment reduced mortality. In our study, the mortality rate was 44% in the patients who received vitamin C treatment and 60% in the control group. Although the difference was not statistically significant due to the sample size in the study, the low mortality rate in the patients who received the vitamin C treatment is a striking finding. We found that vitamin C administration did not reduce the length of ICU stay, and the mean length of stay was 10 days in both groups.

Vitamin C is the cofactor of dopamine β-hydroxylase, a copper-containing enzyme that plays a critical role in the synthesis of noradrenaline from dopamine.[18] For this reason, the effects of HDVC treatment on the vasopressor need of ICU patients have come to the fore. Zabet et al.,[19] showed that vitamin C supplementation reduced the need for vasopressor in their study in septic shock patients who were given vasopressor support. In their published retrospective clinical study, Marik et al.,[20] administered vitamin C, thiamine, and hydrocortisone treatments to patients with sepsis and septic shock in the ICU and found that the need for vasopressor support was significantly reduced in the treatment group. In our study, 34.2% of the patients who received HDVC treatment needed vasopressors, while 55% of the patients in the control group needed vasopressors.

In the studies conducted, the effects of HDVC on the mechanical ventilation duration were evaluated, rather than the mechanical ventilation need. In the CITRIS-ALI study

conducted in ICU patients with septic shock diagnosis, the mean number of days without a ventilator was 10.6 days in the patients who received vitamin C treatment at the beginning and 13.6 days in the control group.[16] In addition, considering that the initial PaO_2/FiO_2 ratio was 190 in the patients in the vitamin C group and 210 in the control group, the positive effects of vitamin C on oxygenation and respiratory mechanics were clearly shown in this study. According to our study, while no significant difference was found between the initial PaO_2/FiO_2 ratios of the groups, this value increased by 31% in the patients who received vitamin C for 96 h and by 20% in the control group. Although these results suggest that vitamin C administration has positive effects on oxygenation, it did not show a positive effect on the need for mechanical ventilation. While the invasive mechanical ventilation requirement was 74% in the patients who received HDVC, it was 75% in the control group. The fact that more negative results regarding the invasive mechanical ventilation requirements were obtained in this study than in other studies may be associated with the different pathogenesis and more aggressive course of COVID-induced ARDS.

During this pandemic period, knowledge of the risk of mortality and severity of the disease in patients followed up in the ICU and progressing with high mortality has become a need for creating both triage and patient-related treatment plans. Although the use of the SOFA scoring system is customary, especially in the case of sepsis, it has a strong predictive value related to the disease mortality and severity in patients followed up in the ICU.[21] Moskowitz et al.,[22] could not find a significant difference between the 0 and 96–h SOFA score changes in the treatment and control groups in their study with a combination of vitamin C, corticosteroid, and thiamine in patients with septic shock. Similarly, in patients with sepsis and acute respiratory failure, vitamin C treatment was administered, and the SOFA score decreased in both the treatment and control groups, but no significant difference was found between these changes in the CITRIS-ALI study.[16] In our study, the initial mean SOFA score was 4.7 in the HDVC group and 4.9 in the control group. In the 96th–h assessment, the score increased by 12% in the HDVC group and by 51% in the control group. Even if we cannot say that vitamin C treatment reduces the SOFA score, on the basis of our findings, a significant difference emerged when we compared the changes between the groups. Unlike in the previous studies in the literature, considering that our study was performed among patients with COVID-19 and that a parallelism exists between the mortality results and SOFA scores, we can infer that vitamin C treatment suppressed the increase in the SOFA scores in the patients with COVID-19.

In our study, the CRP and procalcitonin values were much higher than the normal values at the beginning and 96th h in both groups. The CRP values decreased at the 96th h as compared with those at the beginning in the vitamin C group and increased slightly in the non-vitamin C group. In both groups, the procalcitonin value increased at the 96th h as compared with that at the beginning, and this increase was more distinct in the non-vitamin C group. The high CRP and procalcitonin values observed both at the beginning and during follow-up may be associated with the development of bacterial superinfection, and the necessity of differential diagnosis became a problem. The recognition difficulty in the begining of the pandemic caused the high antibiotic use rates.[23] Recent data obtained in a systematic review indicated that the incidence rate of bacterial infection in patients with COVID-19 was 7% in all the patients and 14% in those hospitalized in the ICU.[24] Routine empirical antibiotic therapy was not administered in our clinic. In case of deterioration in the current clinical findings and increases in CRP and leukocyte values in daily follow-up, with procalcitonin values in the foreground, blood, tracheal aspirate, and urine cultures were performed, and bacterial infection was diagnosed on the basis of the microbiological result. Bacterial infection was detected in only 4% of the patients in our study. The fact that our data included those obtained at the 96th h may have been restrictive in terms of evaluation.

Hu et al.,[25] showed in their study that the procalcitonin values of the patients with COVID-19 increased four-fold in severe disease and eight-fold in critical illness and tended to increase in the mortality cases. In our study, the procalcitonin level increased to approximately four-fold of the reference range at the beginning and eight-fold at the 96th h in both groups, which may indicate a poor prognosis. Many studies that applied HDVC showed that the CRP and procalcitonin levels decreased in severe sepsis.[26,27] In our study, the CRP value decreased after vitamin C treatment, and the increase in the procalcitonin value was less in the vitamin C group than in the non-vitamin C group.

The elevated ferritin level caused by intense inflammation has been associated with both the high mortality and need for intensive.[28,29] The high ferritin levels in COVID-19 have also been shown to be associated with poor prognosis and high mortality.[30] In our study, while the median ferritin level in the patients treated with HDVC decreased from 665 to 620 ug/L, it increased from 553 to 999 ug/L in the control group. In conclusion, although HDVC treatment has positive effects on the laboratory parameters, these effects are not parallel to the clinical course.

Conclusion

Consequently, high-dose vitamin C therapy in acute respiratory failure due to COVID-19 pneumonia did not shorten the length of ICU stay and did not reduce mortality, the invasive mechanical ventilation, and vasopressor requirements. However, high-dose vitamin C treatment had positive effects on the SOFA score and ferritin, procalcitonin, and CRP levels.

Disclosures

Ethics Committee Approval: Sisli Hamidiye Etfal Training and Research Hospital Ethics Committee, Approval No: 3021, 24/11/2020.

Peer-review: Externally peer-reviewed.

Conflict of Interest: None declared.

Authorship Contributions: Concept – N.C., M.A., A.S.C.; Design – N.C., M.A., H.S.T., N.P.; Supervision – N.C., M.A., A.S.C., H.S.T., S.I.; Materials – N.C., M.A., S.I., M.T.O.; Data collection &/or processing – N.C., M.A., S.I.; Analysis and/or interpretation – N.C., M.A., N.P., S.I., M.T.O.; Literature search – N.C., M.A., H.S.T., A.S.C.; Writing – N.C., M.A., H.S.T., A.S.C., S.I., N.P., M.T.O.; Critical review – N.C., M.A., H.S.T., A.S.C.

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