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The use of vitamin C in the intensive care unit during the COVID-19 pandemic

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ABSTRACT

Objectives: An exaggerated inflammatory immune response is observed in cases of COVİD 19. This study aims to evaluate the effects of vitamin C, as a significant modulator of inflammation, on the inflammatory parameters and mortality in patients followed up in the intensive care unit (ICU) during the pandemic.

Methods: This single-center retrospective study included 160 adult patients with confirmed positive nasopharyngeal swab COVID-19 PCR test results, who were followed up in the ICU between 01 March and 01 August 2020. Hospital files were scanned and patients given and not given vitamin C were assigned, to Group 1 and Group 2, respectively. The Acute Physiology and Chronic Health Evaluation (APACHE II) scores, the data entries on demographics, ventilation, laboratory tests, duration of ICU stay, discharge, and mortality were compared. Interventions with antiviral and antibacterial agents. steroids, cytokine apheresis, and renal replacement therapy were evaluated.

Results: Vitamin C treatment was started in patients with raised neutrophil/lymphocyte ratio (NLR) at admission to ICU, who made up 20% of the total 160 ICU patients. Mortality incidence was higher among patients with raised NLR. Vitamin C at the doses used did not affect the inflammatory parameters, length of stay or mortality, and 37.5% of the patients recovered and were discharged from the ICU.

Conclusions: We think that vitamin C treatment will have positive effects on the initiation of COVID-19 and that the time of intiation of the therapy and the optimal doses used should be determined with prospective studies.

Keywords: COVID-19, intensive care, vitamin C, NLR

Given the induction of an exaggerated immune response in coronavirus disease -19 (COVID-19), the use of supplementary therapy with various vitamins has been considered [1-3]. Vitamin C is a water soluble powerful antioxidant agent which is not synthesized and not stored in human body. It has effects on the reduction of gene expression of proinflammatory cytokines and protects the structure and function of DNA, tissue proteins, and lipids [4-7]. It modulates immune response and takes place in lymphocyte proliferation and neutrophil phagocytosis [7]. Vitamin C has been shown to be involved in the control of the immunopathological response augmenting the pathogenesis of severe viral infections of the respiratory

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system [1, 8] and also in the prevention of tissue damage in acute respiratory distress syndrome (ARDS) [1, 9]. In ICU patients and other cases of infections, the systemic vitamin C need increases [10, 11] and intravenous (i.v.) replacement with high doses may be required [8].

The recently increased clinical research on the effect of vitamin C in cases of ARDS and septic shock has produced conflicting reports on the dosages used [1, 2, 5]. Vitamin C has been shown to reduce the severity of multi-organ failure, the levels of circulating biomarkers of tissue damage [2, 10, 12, 13] and the incidence of mortality [14]. Positive effects of 6-24 gm/day i.v. vitamin C have been reported in cases of COVID-19 with serious lung damage [14, 15].

Biomarkers such as D dimer, C-reactive protein (CRP), ferritin, fibrinogen, and IL-6 reach high levels in COVID-19 patients [15, 16]. The effect of vitamin c on lowering the inflammatory production has given hope in the treatment of viral infections [1, 7, 18-20]. It is believed that the timely use of i.v. vitamin C especially inhibits the cytokine storm and improves the outcome in COVID-19 [2]. Research shows that inflammatory parameters neutrophil/lymphocyte ratio (NLR), CRP, D dimer, and troponins are useful to determining the severity of COVID-19 and predicting the prognosis [16]. As an antioxidant and anti-inflammatory nutrient, effects of vitamin C need to be investigated in COVID-19 [7, 17].

Therefore, in this study, we aimed to assess the effects of high dose vitamin c on inflammatory parameters, the duration of ICU stay and mortality in COVID-19 patients admitted to ICU.

METHODS

The approval for this single center retrospective study was given with the Ethics Committee of the Ministry of Health Scientific Research Council by the document numbered and dated 2011-KAEK-25 2020/07-12. Adult patients who had positive nasopharyngeal swab COVID-19 PCR test results and were admitted to the ICU between 01 March 2020 and 1 August 2020 were included in the study. Exclusion criteria were defined as having unconfirmed PCR and pregnancy was accepted as the exclusion criteria. Treatment protocols in the ICU were designed according to the current Ministry of Health guidelines [21]. Vitamin C support was given as 3×2 gm, i.v. Patients were divided into 2 groups as Group 1 and Group 2 on the basis of, receiving and not receiving vitamin C therapy, respectively. Hospital files were scanned for data on demographics including age, gender, blood group, comorbid diseases and also the symptoms at admission to the ICU, the APACHE II scores, invasive ventilation use, oxygen support methods using non breather mask with reservoir, high flow nasal cannula (HFNC), non-invasive ventilation (NIV), duration of hospital stay, and ICU stay, discharge and mortality were recorded. The hematological data on D dimer, procalcitonin, CRP, ferritin, NLR and troponin levels at entry and discharge from the ICU, bacterial cultures, antiviral, antibacterial treatments, use of immune plasma, cytokine apheresis, and renal replacement

Table 1. The characteristics of the patients

	n = 160
Age (year), mean ± SD	70.19 ± 14.41
BMI, mean ± SD	22.55 ± 10.53
Gender, n, (%) Female/Male	72 (45)/88 (55)
Comorbid disease, n (%)	
Non	14 (8.3)
Hypertension	62 (38.8)
Diabetes mellitus	18 (11.3)
KAD-CHF	20 (12.5)
COPD	12 (7.5)
Malignancy	7 (4.4)
Others	22 (13.8)
Arrival symptom	
Fever	40 (25)
Cough	6 (3.8)
Respiratory distress	79 (49.4)
Syncope	7 (4.4)
Arrest	3 (1.9)
Others	18 (11.3)
Given Vitamin C, n (%)	32 (20)
Exitus, n (%)	92 (57.5)

Data are shown as mean ± standard deviation and n (%). KAD-CHF = Coronery arter disease-congestive heart failure, COPD = chronic obstructive pulmonary disease,

therapy (RRT) were evaluated.

Statistical Analysis

Statistical evaluations of the data were carried out using the SPSS 21.0 for Windows (Statistical Package for the Social Sciences, Armonk, NY, USA). The Kolmogorov- Smirnov test was used to determine normality of distribution for the variables. Continuous variables were expressed by the mean, the standard deviation, or the median (minimum-maximum) values, and the categorical data were expressed in percentages. Intergroup comparisons were made using the t test. The Pearson chi-square test was used to detect the differences between groups on the basis of categorical variables. For responses at different time points, percent changes above the baseline measurement were calculated. These percent changes were compared using the Mann-Whitney U test and student t test for the two groups. A $p < 0.05$ was accepted to indicate statistical significance..

RESULTS

The data of the 160 PCR (+) COVID-19 patients were analyzed. The demographic details of the patients are presented in Table 1. Vitamin C treatment was started on 20% of the patients and mortality incidence was determined as 57.5%. There was no statistically significant difference in the duration of ICU stay in the comparison between the groups (Table 1). The data of the two groups on the APACHE II scores, invasive ventilation, use of HFNC, NIV, and nonbreather mask did not differ significantly. The duration of ICU stay, the conditions at discharge and mortality also did not differ significantly between the two groups (Table 2). The NLR value of the patients who were given vitamin C were higher at admission to ICU ($p = 0.028$). The percentage changes at different time points of NLR responses at ICU relative to that at admission did not differ sifnificantly between two groups ($p = 0.18$) (Table 2). The baseline NLR levels of the nonsurviving patients were signifcantly higher as compared to the survivors of ICU treatment ($p = 0.005$). D dimer, procalcitonin, CRP, ferritin, and troponin levels during COVID-19 infection did not differ significantly between both groups (Table 3).

There were no significant differences in terms of steroid use between two groups. Implementations of antiviral, antibacterial, immune plasma treatments, bacterial cultures; the use of cytokine apheresis and RRT, also did not significantly differ between the two groups (Table 4).

Table 2. Comparison of ventilation method, duration of stay and mortality between groups

	Group 1 (n = 32)	Group 2 (n = 128)	*p* value
APACHE II	25.46 ± 7.20	25.40 ± 6.97	0.96
Invasive ventilation	23 (71.9)	91 (71.7)	0.88
HFNC	11 (34.4)	40 (31.3)	0.73
NIV	6 (18.8)	14 (10.9)	0.61
Nonbreather mask with reservoir	25 (78.1)	77(60.2)	0.16
NLR*			
admission	24.83 ± 28.70	13.26 ± 12.58	0.028
discharge	14.93 ± 47.34	14.44 ± 16.47	
discharge Δ	0.34 ± 0.93	-0.54 ± 1.62	0.18
Duration of ICU stay**	8 (2-31)	7(1-47)	0.61
Discharge	12 (37.5)	34 (26.6)	0.20
Mortality	17 (53.1)	75 (58.6)	0.57

Data are shown as mean± standard deviation and n (%). HFNC = high flow nasal cannula, NIV = non-invasive ventilation, NLR = neutrophil/lymphocyte ratio, Δ percent change between ICU admission and discharge, The chi-square test, *Student t test, ** Man Whitney U, median (minimum-maximum)

Table 3. Comparison of inflammation markers between groups

	Group 1 (n = 32)			Group 2 (n = 128)			*p* value
	Median	Minimum	Maximum	Median	Minimum	Maximum	
D Dimer							
admission	2.90	0.32	59.7	3.50	0.25	215.0	0.82
discharge	3.50	0.43	80.0	3.90	0.58	675.0	
discharge Δ	-0.029	-0.98	90.67	-0.033	-0.98	162.27	0.87
CRP							
admission	126.5	3.14	368.0	104.5	3.10	329.0	0.32
discharge	90.90	3.70	393.0	99.0	3.00	364.0	
discharge Δ	0.009	-0.98	101.55	-0.19	-0.98	101.89	0.88
Ferritin							
admission	537.30	21.40	2903.00	714.42	3.70	1245.71	0.30
discharge	293.00	99.0	2669.0	623	41.5	16.830	
discharge Δ	0.51	-0.79	8.5	0.30	-0.83	226.63	0.60
Procalcitonin							
admission	4.5	0.45	29.94	1.71	0.03	86.0	0.26
discharge	4.9	0.09	36.80	0.65	0.04	41.0	
discharge Δ	-0.82	-0.99	40.72	-0.35	-0.99	44.56	0.88
Troponin							
admission	66.8	4.12	3117	103.0	4.15	1600	0.80
discharge	103.0	4.15	4609	103.0	5.82	6259	
discharge Δ	0.48	-0.79	31.86	0.62	-0.83	172.43	0.46

CRP = C-reactive protein, Δ percent change between ICU admission and discharge, Mann-Whitney U test.

Table 4. Comparison of treatment practices and bacterial culture between groups

	Group 1 (n = 32)	Group 2 (n = 128)	*p* value
Antiviral	25 (78.1)	84 (65.6)	0.20
Hydroxychloroquine	31 (96.9)	118 (92.2)	0.34
Antibacterial treatments	25 (78.1)	75 (59.1)	0.46
Steroid	10 (31.3)	37 (28.9)	0.83
Immune plasma	1 (3.1)	13 (10.2)	0.30
RRT	7 (21.9)	23 (18.0)	0.61
Cytokine apheresis	1 (3.1)	7 (5.5)	0.58
Bacterial cultures	18 (56.3)	65 (50.8)	0.69

Data are shown as n (%). RRT = Renal replacement therapy, the chi-square test

DISCUSSION

Although the optimal dosages are not known, high doses of vitamin C have been used for many years for preventing and reducing the severity of respiratory infections without reports regarding serious adverse side effects [1, 7, 14, 18, 19]. The vitamin C levels of COVID-19 patients admitted to ICU were reported by Arvinte *et al*. to be 200% higher in the survivors as compared to the nonsurvivors [22]. In our study, only the NLR values were observed to be significantly higher in the nonsurviving ICU patients in comparison to the survivors. It was seen that the daily use of 6gm vitamin C was started in patients with higher NLR levels at the time of ICU admission. Vitamin C treatment at this dose did not significantly affect the incidence of mortality, length of stay in ICU or the levels of the inflamatuary and biochemical markers such as D dimer, ferritin, troponin and procalcitonin.

In ICU patients and especially in cases of septic shock and renal replacement therapy, vitamin C levels may decrease despite standard nutritional supplementation [10, 11] which needs to be corrected by high (1-4 gm /day) doses of vitamin C [2, 19, 23]. High dose vitamin C support has been shown to reduce the biomarkers of tissue damage in ARDS and sepsis cases [2, 10, 12]. Timely use of this support is believed to inhibit the cytokine storm induced in COVID-19 [2]. The raised levels of the inflammatory parameters such as NLR and D dimer were found to be indicative of the severity and also predictive of the prognosis of COVID-19 [15, 16]. Zang *et al*. [23] showed that the disease severity is increased when CRP levels are > 90 mg/L and D dimer levels are > 1 mg/L by retrospective analysis of the data on 95 COVID-19 patients. In this study, patients started with 6g/day vitamin C dose at admission to ICU and had very high CRP and D dimer levels (113.4 mg/L and 10.9 mg/L, respectively). However, the mean levels of the inflammatory markers did not significantly differ between the two groups of patients in our study.

Raised NLR value is another inflammatory marker used in serious cardiovascular diseases and for mortality prediction in sepsis. It is believed that the abnormal hematopoietic effect of the coronavirus on the bone marrow, peripheral blood cells and the immune response is related to the severity of the COVID-19 infection [16]. In the retrospective study by Yang *et al*. [25] on COVID-19 patients, raised levels of NLR were found to indicate disease severity. The most frequently observed symptoms were fever (83.8%) and cough (70.9%). The most frequently expressed complaints by our patients were respiratory distress (49%) followed by fever (25%). All of our patients had raised NLR and those very high values were started with vitamin C treatment. NLR levels were similar in both groups at discharge from the ICU.

Mortality incidences are increased by the rapid development of COVID-19 pneumonia and ARDS [2]. The World Health Organisation (WHO) does not have a recommendation for the use of vitamin C [26]. In the literature, next to recommendation of daily does of 1-4gm, highest daily dose used was reported as 15 gm [19, 27]. High dose of vitamin C in cases of sepsis and ARDS are believed to reduce the levels of tissue damage markers in the circulation [2, 10, 12]. However, the views on the effect of vitamin C on mortality are variable [12, 28]. In the VITAMINS study on 216 patients, vitamin C (6 gm/day, iv), hydrocortisone (200 mg) and thiamine (400 mg) combination did not show a difference of effect when compared to the use of hydrocortisone alone [28]. In a meta-analysis of the results of 12 studies on a total of 1766 ICU patients, vitamin C treatment was demonstrated to decrease ICU stay by 8% [23]. Another meta-analysis confirmed this result and also showed a reduction of 11% in the use of mechanical ventilation [24]. The multicentred CITRIS-ALI randomised trial on 167 sepsis and ARDS patients were given 50 mg/kg i.v. vitamin C every 6 hours did not change the sequential organ failure assessment (SOFA) score, the levels of inflammatory and vascular damage markers such as CRP and thrombomodulin but reduced the incidence of the 28-day mortality and the days without ventilator use [29]. In the placebo controlled study by Zang *et al*. [30] on 54 patients, with iv. vitamin c at a daily dose of 24 gm for 7 days, the secondary outcome of 28-day mortality dropped from 46.3%.to 29.8%. Our study did not detect any change in mortality rates between two groups. However, it was found that the high NLR level in hospitalization was associated with mortality. In addition, patients who received Vitamin C had higher NLR at hospitalization.

Chiscano-Camón et al. *et al*. [31] found low circulating vitamin C levels in a limited number of patients with ARDS due to COVİD 19. Antiviral agents

were used in 77%, hydroxychloroquine was used in 94% and steroids were used in 55% of the patients and the mean duration of ICU stay was determined as 28.4 days. Vitamin C use was seen to reduce the duration of ICU stay by 7.8 % [29]. In our study, the same treatment protocol was followed for antiviral agents and hydroxychloroquine in both groups. Antiviral and hydroxychloroquine were used in 78.1% and 96.9% of the patient's Group 1, and in 65.6% and 92.2% of the Group 2 patients, respectively. Steroids were used less frequently in our study, being given to 31.3 of group 1 patients and 28.9 of group 2 patients. Steroid treatment had no significant effect on the duration of ICU stay in patients receiving vitamin C therapy.

Limitations

The main limitations of our study are that it was retrospective, single-centered, the duration of mechanical ventilation was not determined, and the blood levels of vitamin C were not measured in the patients. The homogeneity of the data on demographic characteristics and distribution of comorbid diseases and the use of the same treatments for COVID-19 are the strengths of the study.

CONCLUSION

Vitamin C use in COVID-19 patients reduces the oxidative stress and plays an important role in the functioning of immune system. NLR is an important predictor of mortality in these patients, which can be positively affected by vitamin C treatment. Research with varying doses and timings of vitamin C use in the treatment of COVID-19 cases would contribute to the presently limited knowledge on the treatment of this disease and help determine the ICU treatment protocols in any future waves of this viral pandemic and in the cases of sepsis and ARDS.

Authors' Contribution

Study Conception: ŞEÖ, İC, KÖ; Study Design: ŞEÖ, İC, ŞE, HES; Supervision: ŞEÖ, ŞY, İC, ŞE, KÖ, HES, DK; Funding: ŞEÖ, ŞE; Materials: ŞEÖ, İC, KÖ; Data Collection and/or Processing: ŞEÖ, İC, KÖ, HES, ŞE, DK, ŞY; Statistical Analysis and/or Data Interpretation: ŞEÖ, İC, KÖ, HES, ŞE, DK, ŞY; Literature Review: ŞEÖ, İC, KÖ, HES, ŞE, DK, ŞY; Manuscript Preparation: ŞEÖ, İC, KÖ, HES, ŞE, DK, ŞY and Critical Review: ŞEÖ, İC, KÖ, HES, ŞE, DK, ŞY.

Conflict of interest

The authors disclosed no conflict of interest during the preparation or publication of this manuscript.

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