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Original Article

Effects of high dose vitamin C administration in Covid-19 patients

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Abstract

Aim: There is currently no pharmacotherapy with for the treatment of COVID-19. We aimed to investigate the effects of early and high-dose vitamin C (VC) therapy in hospitalized patients with COVID-19.

Materials and Methods: We included patients (n=139) who received high-dose VC supplement to the standard treatment protocol into group 1 (n=58), and only those who received a standard treatment protocol into group 2 (n=81). The patients' requirement for supplemental oxygen therapy, requirement for intensive care treatment and survival rates was investigated retrospectively. Furthermore, the changes in white blood cell, C-reactive protein (CRP), procalcitonin, D-Dimer, renal function tests, ferritin, and interleukin 6 values during hospitalization were evaluated.

Results: When the groups were compared in terms of clinical data, there was no significant difference in terms of the patients requiring supplemental oxygen therapy (p=0.808), requiring intensive care (p=0.662), and survival rates (p=0.185). However, a significant difference was observed between the groups in terms of changes in renal function tests, and CRP values (p<0.05).

Conclusion: In the present study, early administration of high-dose VC to patients with COVID-19 has a reducing effect on the impaired kidney functions. Therefore, we recommend the use of VC as an early supplemental therapy in patients with COVID-19.

Keywords: Ascorbic acid; coronavirus; kidney function tests; severe acute respiratory syndrome; pneumonia

INTRODUCTION

The outbreak caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), which emerged in Wuhan, China, was named as Coronavirus disease 2019 (COVID-19) and declared as a pandemic (1). COVID-19 has a wide clinical spectrum, including asymptomatic infection, upper respiratory tract infection (URTI), pneumonia, acute respiratory distress syndrome (ARDS), and death (2). About 26% of patients with pneumonia findings due to COVID-19 require intensive care due to the development of ARDS and septic shock (3). There is currently no specific treatment or vaccine with proven safety and efficacy for COVID-19. Studies are ongoing to find an effective treatment and to develop a vaccine that provides complete protection against the disease.

Although the treatment protocols of COVID-19 disease differ from country to country, combinations of drugs such as azithromycin, favipiravir, remdesivir, tocilizumab are generally used (2,4). Moreover, some supportive drugs and agents are added to the treatment of patients. One of them is vitamin C (VC), which has been shown to be effective in the treatment of patients developing ARDS (5). Proinflammatory cytokines that increase due to SARS-CoV-2 virus infection cause cytokine storm in the body. This cytokine storm causes the formation of free oxygen radicals and impairs alveolo-capillary membrane permeability, resulting in cellular damage in lungs (6). Antioxidants such as VC, N-acetyl-cysteine, and selenium are effective in preventing this damage. One of the most important parts of the non-enzymatic antioxidant system is VC (7). Vitamin C decreases organ injury caused by cytokines by activating the immune system, and increases survival (8). It is also involved in the synthesis of steroids and catecholamines, wound healing, carnitine synthesis and endothelial cell function (9).

The efficacy of high-dose intravenous VC therapy in COVID-19 has not been clearly demonstrated yet. However, VC, which is used by millions of people, is one

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of the supplements that can be primarily considered in the treatment of COVID-19 disease since it is cost-effective and has a perfect side effect profile (8).

This study aimed to investigate the effects of early and high-dose supplemental VC therapy in hospitalized patients with COVID-19 diagnosis.

MATERIALS and METHODS

Ethics Approval (No. 2020/106) was obtained from the local ethics committee of our hospital. The files of the patients who received inpatient treatment with the diagnosis of COVID-19 between March and May 2020 were reviewed retrospectively. The study included patients between the ages of 18–99 years who were diagnosed with COVID-19 by an infectious diseases specialist through polymerase-chain-reaction (PCR) and high-resolution computed tomography (HRCT). In our hospital, patients diagnosed with COVID-19 are treated with the combination of hydroxychloroquine - azithromycin - favipiravir as the standard treatment protocol. However, high-dose intravascular VC therapy was administered to patients hospitalized before April 20 in addition to the standard treatment protocol. After April 20, VC was excluded from the treatment protocol to reduce the drug burden considering the possible negative effects of high-dose VC on kidney functions. The patients were divided into two groups as Group 1 including patients who received high-dose VC in addition to the standard treatment protocol and Group 2 including patients who only received the standard treatment protocol. The demographic data of the patients including age, gender, weight, height, body mass index (BMI) were analyzed. Length of hospital stay, requirement for supplemental oxygen therapy, requirement for intensive care therapy, and survival rates were compared as well. Furthermore, the changes in white blood cell (WBC), C-reactive protein (CRP), procalcitonin (PCT), D-Dimer, urea, creatinine, ferritin, and interleukin 6 (IL-6) values during hospitalization were evaluated.

Hydroxychloroquine 2x200 mg following a loading dose of 2x400 mg, azithromycin 1x250 mg following a loading dose of 1x500 mg, and favipiravir 2x600 mg following a loading dose of 2x1600 mg were administered to patients in Group 2 for five days. Intravenous VC therapy was administered to the patients in Group 1 at a dose of 25 g/day for seven days in addition to these drugs. Kidney function test values were followed to monitor the negative effect of high-dose VC administration on kidneys and electrolytes. VC therapy was discontinued in the patients whose kidney functions were found to be impaired.

Statistical Analysis

Statistical analysis of all data was performed using SPSS version 25.0 software (Statistical Package for Social Sciences Inc; Chicago, IL, USA). The Kolmogorov-Smirnov test was used to determine normality of continuous data. Normally distributed continuous data were expressed as mean ± standard deviation. The independent-samples t-test was used to compare continuous data in independent groups. Discrete data were expressed as number and percentage. The chi-square test was used to compare discrete data in independent groups. Fischer's exact test was used in cases where the expected cell count was more than 20% of the total cell count, whereas Pearson Chi-Square test was used in cases where the expected cell count was less than 20% of the total cell count. In the intragroup comparison of continuous parameters measured at different times, the Paired Samples t-test and Wilcoxon test were used for normally distributed and non-normally distributed parameters, respectively. A p-value of <0.005 was considered statistically significant.

RESULTS

The data of 139 patients treated for COVID-19 in our hospital between March and May were retrospectively analyzed. While 58 patients (group 1) were treated with the standard treatment protocol + VC therapy, 81 patients (group 2) were treated with the standard treatment protocol only. Table 1 and Table 2 present the demographic data (e.g. age, height, weight, gender) of the patients in group 1 and group 2, length of hospital stay, presence of comorbidities, and data on the presence of HRCT findings. When the demographic data were evaluated, there was a statistically significant difference between groups in terms of weight (p=0.001), BMI (p=0.007) and gender (p=0.038), while there was no significant difference in terms of height, and age (Table 1, Table 2).

Table 1. Comparison of demographic data and length of hospital stay by groups (mean ± SD)

	Group 1 n=58	Group 2 n=81	p*
Age (year)	56.53 ± 18.77	62.20 ± 15.72	0.056
Height (cm)	167.46 ± 8	169.19 ± 6.74	0.172
Weight (kg)	75.02 ± 9.62	80.91 ± 10.34	**0.001**
BMI (kg/m²)	26.77 ± 3,20	28.22 ± 2.82	**0.007**
Length of hospital stay (day)	12.95 ± 7.74	13.44 ± 6.03	0.678

*Independent sample T test

Table 2. Comparison of demographic and clinical data by groups

	Group 1 n=58		Group 2 n=81		p*
	n	%	n	%	
Presence of comorbidities					
1	38	65.5	52	64.2	0.872
2	20	34.5	29	35.8	
Gender					
Male	27	46.6	52	64.2	**0.038**
Female	31	53.4	29	35.8	
HRCT					
Typical	41	70.7	49	60.5	0.215
Not Typical	17	29.3	32	39.5	

*Chi-square test

Twenty-six patients (44.8%) in Group 1 and 38 (46.9%) patients in Group 2 were observed to receive supplemental oxygen therapy and there was no statistically significant difference between the groups in this regard (p=0.808) (Table 3).

Table 3. Comparison of clinical data by groups

	Group 1 n=58		Group 2 n=81		p*
	n	%	n	%	
Supportive Oxygen Treatment					
Yes	26	44.8	38	46.9	0.808
No	32	55.2	43	53.1	
Intensive Care					
Yes	18	31	28	34.6	0.662
No	40	69	53	65.4	
Exitus	6	10.3	15	18.5	0.185
Discharge with Cure	52	89.7	66	81.5	
Impaired Kidney Function Test					
Yes	6	10.3	23	28.4	0.010
No	52	89.7	58	71.6	

*Chi-square test

It was observed that 18 patients (31%) in Group 1 and 28 patients (34.6%) in Group 2 required intensive care and there was no statistically significant difference between groups in this regard (p=0.662) (Table 3).

Six (10.3%) patients in Group 1 and 15 (18.5%) patients in Group 2 died and there was no statistically significant difference between the groups in terms of mortality rates (p=0.185) (Table 3).

Impaired kidney function test values were observed in six patients (10.3%) in Group 1 and 23 patients (28.4%) in Group 2. There was a statistically significant difference between the groups in terms of changes in kidney function values (p=0.010) (Table 3).

Table 4. Changes in CRP, PCT, D-Dimer, urea, creatinine, ferritin, IL-6, and WBC values of Group 1 patients

	Z	p*
CRP (mg/L)	-2.545[b]	**0.011**
PCT (ng/mL)	-0.889[c]	0.374
D-Dimer (ng/mL)	-0.346[c]	0.729
Urea (mg/dL)	-0.260[b]	0.795
Creatinine (mg/dL)	-2.852[b]	**0.004**
Ferritin (ng/mL)	-1.449[c]	0.147
IL-6 (pg/mL)	-0.356[c]	0.722
WBC (mm3)	-	0.724**

WBC: White blood cell, CRP: C-reactive protein, PCT: Procalcitonin
* Wilcoxon test ; ** Paired samples t test

The changes in the WBC, CRP, PCT, D-Dimer, urea, creatinine, ferritin, and IL-6 values, were evaluated within each group. The change in the CRP (p=0.011) and creatinine (p=0.004) values in Group 1 was statistically significant, whereas there was no significant change in the WBC, PCT, D-Dimer, urea, ferritin, and IL-6 values (Table 4). Group 2 had no statistically significant change in any of WBC, CRP, PCT, D-Dimer, urea, creatinine, ferritin, and IL-6 values (Table 5).

Table 5. Changes in WBC, CRP, PCT, D-Dimer, urea, creatinine, ferritin, and IL-6 of Group 2 patients

	Z	p*
WBC (mm^3)	-0.343[b]	0.732
CRP (mg/L)	-0.989[b]	0.323
PCT (ng/mL)	-0.384[c]	0.701
D-Dimer (ng/mL)	-0.558[b]	0.577
Urea (mg/dl)	-1.719[b]	0.086
Creatinine (mg/dL)	-1.028[c]	0.304
Ferritin (ng/mL)	-1.028[c]	0.304
IL-6 (pg/mL)	-1.678[c]	0.093

WBC: White blood cell, CRP: C-reactive protein, PCT: Procalcitonin; * Wilcoxon test

DISCUSSION

The present study shows that high-dose VC therapy administered in addition to standard antiviral therapy does not have a significant effect on requirement for intensive care therapy and mortality rates in patients with COVID-19. However, kidney functions were observed to be better in patients with COVID-19 receiving VC compared to patients receiving standard therapy alone.

In the clinical picture of COVID-19 pneumonia and associated ARDS, increased oxidative stress due to the rapid release of free oxygen radicals and cytokines leads to intensive cellular infiltration, lung damage at the tissue level, and increased alveolocapillary membrane permeability (4). Vitamin C, also known as ascorbic acid, is one of the antioxidant agents that can be given exogenously to prevent damage caused by free oxygen radicals that form due to various reasons in the body (9,10). Hoang et al. defined a dose of ≥10 g / day and above for high-dose vitamin C therapy (11). Correspondingly, we applied high-dose VC to our first group of patients in accordance with these values and the protocol established by the Ministry of Health (12). In the relevant literature, there are studies showing that high-dose VC administration reduces the development of organ dysfunction, severe sepsis, and septic shock in intensive care patients who develop ARDS (13-15). The patients included in the present study consisted of patients with early-stage COVID-19. Therefore, we evaluated that early high-dose VC administration had no effect on requirement for intensive care and survival.

Vitamin C, a water-soluble vitamin, should be taken continuously since it cannot be stored by the body, and when it is taken more than necessary, it is eliminated through the urinary system. If high amounts of VC are taken for a long period of time, it may increase the levels of oxalate in serum and urine and cause urinary system problems such as hyperoxaluria, calcium oxalate crystalluria, calcium oxalate accumulation, kidney stone formation, tubulointerstitial nephropathy, and acute kidney failure (16,17). Therefore, VC should be used with caution on individuals with impaired kidney functions and kidney stones. In the present study, VC was not administered to patients with urinary tract problems. Furthermore, VC therapy was discontinued in patients whose kidney functions were found to be impaired during the treatment process. In contrast to the literature, it was found at the end of the study that kidney function values of patients receiving VC were better preserved and no urinary complications developed in these patients. This may be attributed to the fact that the duration of VC therapy administered to the patients was not long and the kidney function values were well monitored.

Early diagnosis and treatment are of great importance for the course of COVID-19. COVID-19 diagnosis is made based on the detection of the genetic material of the virus, clinical symptoms, and radiological imaging (1). Follow-up of laboratory values is extremely important in terms of following up the course of the disease and arranging treatment. Although the frequency varies depending on the general condition of the patient, the tests recommended for COVID-19 disease are as follows: hemogram, total and subpopulation lymphocyte counts to follow the development of lymphopenia, D-dimer, kidney, and liver function tests for susceptibility to coagulation (creatinine kinase, lactate dehydrogenase, electrolytes), myocardial enzymes, CRP, PCT, ferritin, IL-4, and IL-6 (1). Lymphopenia, increased CRP, LDH, troponin-I, IL-6 levels and increased coagulation are indicators of poor prognosis in the course of the disease (18). In this study, laboratory tests of WBC, CRP, PCT, D-dimer, ferritin, IL-6, urea and creatinine were repeated every other day in both patients groups. However, only the laboratory values of the patients on the first and last day of their hospitalization were statistically evaluated. No statistically significant change was observed in the values except for CRP during clinical follow-up of patients received and not received VC. This change in the CRP value was not clinically significant.

LIMITATIONS

There are some limitations to this study. The retrospective design of the study can be considered as the first limitation. Although CBC and routine biomarkers were monitored daily since the admission of patients to the hospital, proinflammatory markers such as IL-6, CRP, and D-Dimer were not monitored with a standard day protocol. Although there was a difference in mortality rates among patient groups, this difference was found statistically insignificant; this may be due to insufficient sample size. Nevertheless, to our knowledge, this is one of the first studies to investigate the effects of high-dose CV therapy in Covid-19 patients who have potential to need intensive care therapy.

CONCLUSION

In conclusion, the present study showed that early administration of high-dose VC to patients with COVID-19 had no effect on requirement for supplemental oxygen therapy, intensive care therapy, and mortality rates. However, it can be suggested that it has a reducing effect on impaired kidney functions that may occur due to the disease and drugs used. There is a need for comprehensive clinical trials to confirm our findings regarding the positive effects of early use of VC on kidneys among patients with COVID-19, and more data are needed to help VC to be included in the guidelines for the treatment of COVID-19 in the future.

Competing Interests: The authors declare that they have no competing interest.

Financial Disclosure: There are no financial supports.

Ethical Approval: Our study has ethics committee permission and Ethics Approval (No. 2020/106) was obtained from the local ethics committee of our hospital.

REFERENCES

1. Zhou F, Yu T, Du R, et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. Lancet 2020;395:1054-62.
2. Surviving Sepsis campaign. Covid19-Ssc 2020. 2020;2019.
3. Wang D, Hu B, Hu C, et al. Clinical Characteristics of 138 Hospitalized Patients with 2019 Novel Coronavirus-Infected Pneumonia in Wuhan, China. JAMA - J Am Med Assoc 2020;323:1061-9.
4. Carr AC. A new clinical trial to test high-dose vitamin C in patients with COVID-19. Crit Care 2020;24:1-2.
5. Fowler III AA, Kim C, Lepler L, et al. Intravenous vitamin C as adjunctive therapy for enterovirus/rhinovirus induced acute respiratory distress syndrome. World J Crit Care Med 2017;6:85.
6. Carr AC, Rosengrave PC, Bayer S, et al. Hypovitaminosis C and vitamin C deficiency in critically ill patients despite recommended enteral and parenteral intakes. Crit Care 2017;21:1-10.
7. Bolignano D, Cernaro V, Gembillo G, et al. Antioxidant agents for delaying diabetic kidney disease progression : A systematic review and meta-analysis 2017;1-16.
8. Manuel R, Colunga L, Berrill M, et al. Quercetin and Vitamin C : An Experimental , Synergistic Therapy for the Prevention and Treatment of SARS-CoV-2 Related Disease (COVID-19) 2020;11:1-11.
9. Nabzdyk CS, Bittner EA. Vitamin C in the critically ill - indications and controversies. World J Crit Care Med 2018;7:52-61.

10. Review D. New Coronavirus (2019-nCoV / COVID-19) and Vitamin C Yeni Koronavirüs (2019-nCoV / COVID-19) ve Vitamin C 2020;40:2-6.
11. Hoang BX, Shaw G, Fang W, et al. Possible application of high-dose vitamin C in the prevention and therapy of coronavirus infection. J Glob Antimicrob Resist 2020;23:256-62.
12. COVID-19 (SARS-CoV-2 Infection) Guide. Republic Of Turkey Ministry Of Health, Directorate General Of Public Health. 2020;2 Nisan 2020:25.
13. Fowler AA, Truwit JD, Hite RD, et al. Effect of Vitamin C Infusion on Organ Failure and Biomarkers of Inflammation and Vascular Injury in Patients with Sepsis and Severe Acute Respiratory Failure: The CITRIS-ALI Randomized Clinical Trial. JAMA - J Am Med Assoc 2019;322:1261-70.
14. Marik PE, Khangoora V, Rivera R, et al. Hydrocortisone, Vitamin C, and Thiamine for the Treatment of Severe Sepsis and Septic Shock: A Retrospective Before-After Study. Chest 2017;151:1229-38.
15. Teng J, Pourmand A, Mazer-Amirshahi M. Vitamin C: The next step in sepsis management? J Crit Care 2018;43:230-4.
16. Auer BL, Auer D, Rodgers AL. Relative hyperoxaluria, crystalluria and haematuria after megadose ingestion of vitamin C. Eur J Clin Invest 1998;28:695-700.
17. Lamarche J, Nair R, Peguero A, et al. Vitamin C-Induced Oxalate Nephropathy. Int J Nephrol 2011;2011:1-4.
18. Huang C, Wang Y, Li X, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet 2020;395:497-506.