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Outcomes of High-Dose Vitamin C Therapy on Patients Diagnosed with COVID-19 Associated ARDS in Intensive Care Units: Multi-Center Retrospective Study

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ABSTRACT

Background and Aim: The new type of Severe Acute Respiratory Syndrome Coronavirus 2 (Coronavirus 2019- COVID-19) infection is the largest pandemic in the last decade. Acute respiratory distress syndrome is the complication with the highest mortality rate of this infection and there is no adequate treatment with proven efficacy to reduce mortality. This multi-center, retrospective study aimed to determine the effect of high-dose vitamin C on survival and other endpoints in invasively ventilated ARDS patients.

Methods: This multi-center, observational retrospective cohort study was performed at five ICU centers between March 2020 and July 2020. Patients with ARDS due to COVID-19 who required IMV were included. High-dose vitamin C group was defined as patients who were treated with vitamin C over 200 mg/kg for four days. Patients who were not given vitamin C treatment were defined as the control group by using propensity score match analysis, as well. The groups were compared about the effects of high-dose vitamin C treatment on ICU mortality.

Result: A total of 86 patients with a mean age of 67.85 ± 10.38 were included in the study. 72.1% of the patients were male. Forty-two (49%) patients were in the high dose vitamin C group, and 44 (51%) were in the control group. The mean PaO2/FiO2 at the time of admission to the ICU was 128.27±58.69 mmHg (133.63±56.51 mmHg in the control group, 122.36±61.18 mmHg in the study group, p=0.389). The mortality rate of high dose vitamin C group was lower than the control group (73.8% vs. 90.9%, p = 0.037,respectively).

Conclusion: As an adjunctive therapy in invasively ventilated patients with COVID-19-associated ARDS, high doses of vitamin C may reduce mortality and development of organ damage. Prospective, randomized controlled studies with larger numbers of patients are needed to confirm these findings.

Keywords: COVID19, High Dose Vitamin C, ARDS, ICU, Mortality

Introduction

At the end of 2019, the novel coronavirus 2019 (2019-nCoV) was recognized as responsible for a cluster of pneumonia cases in China. 2019-nCoV has high genetic similarity with SARS-CoV. This virus causes COVID-19, a systemic viral infection, especially severe pneumonia (1). COVID-19 quickly spread around the world. Thereupon, the World Health Organization declared this disease a global epidemic (2). Although SARS-CoV-2 is a viral infection that causes multi-organ involvement, the lung is the most prominently affected organ in most cases (3). Due to the aggravation of pneumonia, patients may proceed to respiratory failure, that is called ARDS which has more than 50% mortality (4). Treatment options for COVID-19 are very limited and controversial (5). In addition to some antiviral drugs used in the treatment of severe pneumonia due to COVID-19, supportive treatments are crucial. Some studies have found that vitamin C reduces systemic inflammation in various ways, including attenuation of cytokine elevation and prevention of lung injury in severe sepsis and ARDS (6,7). Vitamin C has essential physiological functions as both an antioxidant and a cofactor for many enzymes. Vitamin C can increase microbial killing. It does this by accumulating in phagocytic cells such as neutrophils, increasing chemotaxis phagocytosis, generation of reactive oxygen radicals (8,9). The shift from spectrophotometric and enzymatic methodologies to high-performance liquid chromatography (HPLC) has greatly improved

variability and interlaboratory agreement, but few centers for vitamin c measurement in daily practice (10).There is limited data supporting the use of vitamin C in sepsis and ARDS. It has been shown in an animal model of sepsis that vitamin C can inhibit pro-inflammatory and procoagulant processes that induce lung injury (6). In a meta-analysis, it was reported that vitamin C used in the critical illness process reduced the length of stay in the intensive care unit and the length of stay on mechanical ventilator (11). Although Vitamin C is used as supportive therapy in the ARDS due to COVID-19, there is no sufficient evidence to demonstrate its effectiveness.

Objectives

This multi-center, retrospective study aimed to determine the effect of high-dose vitamin C on survival and other endpoints in invasively ventilated ARDS patients.

Material-Method

The study was approved by the ethics committee was obtained from the Ethics Committee of Kayseri City Hospital with the date of 12.11.2020 and decision number 222.

This study was conducted retrospectively in five different ICU in five different centers. The distribution of patients by centers was summarized in Supplementary Table 1. The hospital records of the patients who were intubated with the diagnosis of COVID-19 in ICUs between March 11 2020 and July 1 2020 in these centers were retrospectively evaluated. A total of 86 patients from 5 centers were included in the study. Among these, 42 patients were included in the high-dose vitamin C group (study group), and 44 patients were included in the control group. Data of enrolled patients were collected from patient files and electronic hospital records. The collected data include complete blood count, liver function tests, kidney function tests, C-Reactive Protein (CRP), procalcitonin, coagulation tests, arterial blood gas parameters, and ICU outcomes.

Inclusion criteria

- Those with ARDS with COVID-19 who are intubated in the intensive care unit
- Those who have a minimum stay of 48 hours in the intensive care unit

Exclusion criteria

- Patients under 18 years of age
- Pregnant patients
- Patients with known chronic renal failure
- Patients with acute renal failure

Randomization

Patients who were intubated in ICU with the diagnosis of COVID-19 between March 11, 2020 and July 1, 2020, were defined as the study group, and those who did not receive vitamin C treatment over 200 mg/kg for four days using the propensity score match analysis.

Definition of high-dose vitamin C

Vitamin C was prescribed between 20 mg/kg/day – 600 mg/kg/day doses according to the clinician's preference. Although it is not clear which dose can account for the high vitamin C dose, 4*50mg/kg/day (200/mg/kg/day) dose has been accepted as high-dose vitamin C in ARDS according to the literature [1, 2]. In this study, prescription of vitamin C equal to or above 200/mg/kg/day for at least 4 days was accepted as high-dose vitamin C and those included in the study group.

Statistical Analysis

In order to understand whether the data is normally distributed; Histogram, q-q graphs and Shapiro-Wilk test were applied. The homogeneity of variance was checked with the Levene test. Mauchly's test was conducted to test the sphericity assumption. The cumulative sum of Schoenfeld residuals was used to assess the proportional hazard assumption. To compare the differences between groups, an independent samples *t* test or Mann-Whitney U test was applied for continuous variables, while Pearson chi-square or Fisher's exact test were applied for categorical variables. One-way repeated measures analysis of variance (ANOVA) was used for within-group comparisons. Bonferroni test was applied for multiple comparisons. To identify the effect of each variable on the survival time of Covid-19 patients, univariate and multiple Cox proportional hazards regression methods were performed. Three separate models were fitted. Model-1 explores the individual effects of each variable on survival time. Model-2 explores the effect of each variable on survival time after adjustment by age, gender and APACHE II score. Significant variables at $p<0.05$ were included in a multiple model and forward elimination was performed using likelihood ratio statistic. Model-3 explores the effect of these independent risk factors obtained from the multiple model. Hazard ratios are calculated using 95% confidence intervals. Kaplan-Meier plots were generated and Log-rank test was conducted to compare the survival probabilities between study groups. All analyses were conducted using R 4.0.1 (www.r-project.org) and TURCOSA (www.turcosa.com.tr) statistical software.

Results

A total of 86 patients were included in our study, 44 ,were in the control group and 42 were in the high-dose vitamin C group (study group). The mean age of the patients was 67.85±10.38 years (71.39±9.50 in the control group and 64.14±10.07 in the study group). 72.1% of the patients were male, and 27.9% were female. The median Acute Physiology and Chronic Health Evaluation-II (APACHE-II) score at the time of admission to the ICU was 19.5 (15.0-26.0) [22.0 (15.5-29.0) in the control group, and 18.0 (13.0-24.0) in the study group (p=0.035)]. The mean Sequential Organ Failure Assessment (SOFA) score at the time of admission to the ICU was 6.85±3.10 (5.90±3.28 in the control group, 7.79±2.63 in the study group, p=0.005). The mean PaO_2/FiO_2 at the time of admission to the ICU was 128.27±58.69 mmHg (133.63±56.51 mmHg in the control group, 122.36±61.18 mmHg in the study group, p=0.389). At the time of admission, the mean pH value was 7.35±0.12 (7.38±0.10 in the control group, 7.32±0.14 in the study group, p=0.028).

Table 1. Baseline demographic characteristics, clinical, laboratory and intensive care unit results of patients

Variable	Groups		Total (*n*=86,%)	p
	Control (*n*=44,%)	High-Dose Vitamin C (*n*=42,%)		
Age (years)*	71.39±9.50	64.14±10.07	67.85±10.38	**0.001**
Gender (male)	30 (68.2)	32 (76.2)	62 (72.1)	0.408
Body mass index (kg/m²)*	28.09±4.19	26.63±3.26	27.37±3.81	0.076
Underlying conditions				
Diabetes (present)	12 (27.3)	12(28.6)	24(27.9)	0.893
Hypertension (present)	15 (34.1)	18(42.9)	33(38.4)	0.403
CAD (present)	7 (15.9)	2(4.8)	9(10.5)	0.157
COPD (present)	3 (6.8)	3(7.1)	6(7.0)	0.999
CVA (present)	1 (2.3)	1(2.4)	2(2.3)	0.999
Malignancies (present)	2 (4.5)	6(14.3)	8(9.3)	0.152
Charlson Comorbidity Index**	1 (0-1)	1 (0-1)	1 (0-1)	0.862
APACHE-II score**	22.0 (15.5-29.0)	18.0 (13.0-24.0)	19.5 (15.0-26.0)	**0.035**
SOFA score*	5.90±3.28	7.79±2.63	6.85±3.10	**0.005**
Fibrinogen in the first 24* hours (mg/dL)	5392.93±1987.86	5982.20±1583.28	5677.16±1817.77	0.136
Ferritin in the first 24 hours (mg/dL)**	464 (204-971)	673 (277-1371)	591 (247-1178)	0.265
Oxygenation parameters				
FiO_2 (%)*	63.37±19.63	70.49±20.86	66.66±20.39	0.120
$PaO_2/FİO_2$ (mmHg)*	133.63±56.51	122.36±61.18	128.27±58.69	0.389
SpO_2 (%)*	90.60±5.09	90.39±7.94	90.49±6.60	0.884
PaO_2 (mmHg)*	79.56±31.27	75.58±25.09	77.61±28.33	0.518
Lactate (mmol/L)**	1.30 (1.00-2.00)	1.30(0.90-1.78)	1.30 (1.00-1.88)	0.475
pH	7.38±0.10	7.32±0.14	7.35±0.12	**0.028**
Laboratory parameters				
CRP (mg/L)**	89.70 (40.04-177.65)	33.03 (18.97-98.94)	65.35 (22.00-145.00)	**0.004**
WBC (10^3/µL)**	10.67 (7.12-17.30)	12.10 (8.70-16.67)	11.45 (7.65-17.00)	0.528
Lymphocyte (10^3/µL) **	0.70 (0.60-1.40)	0.70 (0.40-1.00)	0.70 (0.50-1.03)	0.221
N/L**	10.84 (5.28-20.61)	15.25 (9.70-23.80)	13.81 (6.98-23.56)	0.141
PCT (ng/ml)**	0.34 (0.17-1.34)	0.41 (0.13-1.12)	0.34 (0.14-1.12)	0.858
Net fluid balance (cc)**	900 (600-1740)	900 (400-1548)	900 (490-1612)	0.707
Vasopressor requirement (yes)	33 (75.0)	34 (81.0)	67 (77.9)	0.506
RRT requirement (yes)	16 (36.4)	6 (14.3)	22 (25.6)	**0.019**
Requirement for Prone position (yes)	8 (18.2)	23 (54.8)	31 (36.0)	**<0.001**
Duration of MV (day)**	11.0 (6.5-17.0)	10.0 (7.0-18.0)	11.0 (7.0-17.0)	0.921
Duration of ICU (day)**	13.0 (9.0-17.0)	15.0 (8.0-24.0)	14.0 (8.0-20.0)	0.385
Duration of hospital stay (day)**	15.0 (10.5-22.5)	23.5 (14.0-34.0)	19.0 (11.0-29.0)	**0.016**
Place from the admission to ICU				
Emergency department	11 (25.0)	11 (26.2)	22 (25.6)	0.929
In-patient clinic	23 (52.3)	23 (54.8)	46 (53.5)	
Out-patient clinic	5 (11.4)	3 (7.1)	8 (9.3)	
Other hospital	5 (11.4)	5 (11.9)	10 (11.6)	

CAD: Coronary Artery Disease; **COPD:** Chronic Obstructive Pulmonary Disease; **CVA:** Cerebrovascular Accident; **APACHE:** The Acute Physiology and Chronic Health Evaluation; **SOFA:** Sequential Organ Failure Assessment; **FiO_2:** Fraction of Inspired Oxygen; **$PaO_2/FİO_2$ Ratio:** Arterial PaO_2/Fraction of Oxygen; **PaO_2:** Partial Pressure of O_2; **CRP:** C-Reactive Protein; **WBC:** White Blood Cell; **L:** Lymphocyte; **N/L:** Neutrophil/Lymphocyte; **PCT:** Procalcitonin; **RRT:** Renal Replacement Therapy; **MV:** Mechanical Ventilation; **ICU:** Intensive Care Unit; *Mean±Standart Deviation; **Median (1st-3rd quartiles), significant p values are shown in bold characters.

There was no difference between the groups in terms of FiO_2, PaO_2, lactate and oxygen saturation values at the time of admission. The prone position was applied to 36% of the patients (18.2% in the control group vs. 54.8% in the study group, p=0.001). During the hospitalization, 25.6% of the patients needed renal replacement therapy (RRT) (36.4% in the control group and 14.3% in the study group, p=0.019). During the hospitalization, 77.9% of the patients needed vasopressors (75.0% in the control group and 81.0% in the study group, p=0.506). The baseline demographic and clinical characteristics of the patients were summarized in Table 1. Mortality developed in 82.6% of the patients during their hospitalization (90.9% in the control group vs. 73.8% in the study group, p=0.037). The statistical difference in mortality was also demonstrated with Cox regression analysis, and this difference persisted even when adjusted for age, sex, and APACHE-II score.

Table 2. Univariate and multiple Cox regression analysis results in predicting the survival

Variable	Model-1 (crude)		Model-2 (adjusted*)		Model-3 (multiple)	
	HR(95%CI)	p	HR(95%CI)	p	HR(95%CI)	p
Age (years)	1.03(1.01-1.06)	0.011	1.03(1.01-1.05)	0.019	1.06(1.02-1.10)	0.003
Gender (male/female)	1.22(0.71-2.12)	0.471	1.15(0.66-1.99)	0.630	-	-
Body mass index (kg/m^2)	1.03(0.97-1.10)	0.355	1.04(0.96-1.13)	0.306	-	-
High-dose vitamin C intake (yes/no)	0.50(0.31-0.81)	0.005	0.57(0.34-0.96)	0.036	-	-
Underlying conditions						
Diabetes (present/absent)	0.97 (0.58-1.64)	0.922	0.88 (0.49-1.57)	0.665	-	-
Hypertension (present)	0.97 (0.59-1.58)	0.888	0.83 (0.50-1.37)	0.454	-	-
CAD (present/absent)	1.49 (0.70-3.18)	0.301	1.19 (0.54-2.63)	0.675	-	-
COPD (present/absent)	0.99 (0.39-2.51)	0.980	0.69 (0.26-1.87)	0.470	-	-
CVA (present/absent)	0.34 (0.05-2.45)	0.282	0.34 (0.05-2.50)	0.292	-	-
Malignancies (present/absent)	0.98 (0.45-2.15)	0.966	1.43 (0.62-3.30)	0.405	-	-
APACHE-II score	1.02 (0.99-1.05)	0.303	1.01 (0.98-1.04)	0.499	-	-
SOFA score	0.92 (0.84-0.99)	**0.046**	0.91 (0.83-0.99)	**0.034**	-	-
Fibrinogen in first 24 hours (mg/dL)	1.00 (0.99-1.01)	0.616	1.00 (0.99-1.01)	0582	-	-
Ferritin in first 24 hours (mg/dL)	1.00 (0.99-1.01)	0.716	1.00 (0.99-1.01)	0.396	-	-
Oxygenation parameters						
FiO_2 (%)	1.00 (0.99-1.01)	0.960	1.00 (0.99-1.01)	0.997	-	-
PaO_2/FiO_2 (mmHg)	1.00 (0.99-1.01)	0.296	1.00 (0.99-1.01)	0.308	-	-
SpO_2 (%)	1.00 (0.97-1.04)	0.948	1.00 (0.96-1.04)	0.901	-	-
PaO_2 (mmHg)	1.00 (0.99-1.01)	0.661	1.00 (0.99-1.01)	0.984	-	-
Lactat (mmol/L)	0.99 (0.88-1.11)	0.851	0.99 (0.88-1.12)	0.902	-	-
pH	1.50 (0.24-9.21)	0.664	1.00 (0.14-7.29)	0.997	-	-
Laboratory parameters						
CRP (mg/L)	1.01(1.00-1.02)	**<0.001**	1.01(1.00-1.02)	**0.001**	1.01(1.00-1.02)	**0.014**
WBC (10^3/µL)	1.00 (0.97-1.02)	0.731	1.00 (0.97-1.03)	0.857	-	-
Lymphocyte (10^3/µL)	1.20 (0.92-1.57)	0.173	1.21 (0.94-1.56)	0.141	-	-
N/L	1.00 (0.98-1.02)	0.724	1.00 (0.98-1.02)	0.709	-	-
PCT (ng/ml)	1.02 (1.00-1.04)	**0.021**	1.01 (0.99-1.03)	0.314	-	-
Net fluid balance (cc)	1.00 (0.99-1.01)	0.937	1.00 (0.99-1.01)	0.682	-	-
Vasopressor requirement (yes/no)	2.25 (1.18-4.28)	**0.013**	2.22 (1.14-4.31)	**0.019**	-	-
RRT requirement (yes/no)	1.49 (0.89-2.50)	0.127	1.36 (0.78-2.37)	0.276	-	-
Prone position requirement (yes/no)	0.69 (0.42-1.12)	0.133	0.78 (0.47-1.29)	0.335	-	-

CAD: Coronary artery disease; **COPD:** Chronic obstructive pulmonary disease; **CVA:** Cerebrovascular accident; **APACHE-II:** The Acute Physiology and Chronic Health Evaluation-II; **SOFA:** Sequential Organ Failure Assessment; **FiO_2:** Fraction of Inspired Oxygen; **PaO_2/FiO_2 ratio:** arterial PaO_2/Fraction of oxygen; **PaO_2:** partial pressure of O2; **CRP:** C-reactive Protein; **WBC:** white blood cell; **L:** lymphocyte; **N/L:** neutrophil/lymphocyte; **PCT:** procalcitonin; **RRT:** Renal replacement therapy; **HR:** Hazard ratio; **CI:** Confidence interval. Significant p values are shown in bold characters. *Adjusted by age, gender and APACHE II score.

Table 3. The comparison of survival variables between groups

Survival variable	Groups		Total (*n*=86)	p
	Control (*n*=44)	High-Dose Vitamin C (*n*=42)		
Number of survival events, n (%)	40 (90.9)	31(73.8)	71(82.6)	**0.037†**
Survival time, median (95% CI)	15.00 (12.39-18.61)	28.00 (21.22-34.78)	20.00 (17.19-34.78)	**0.003‡**

Significant p values are shown in bold characters. P values are obtained using †Pearson chi-square and ‡Log-rank tests

Additionally, the median life expectancy of the hospitalized patients was 20 days when the hospital stay was considered (15 days in the control group vs. 28 days in the study group, p=0.003). In the univariate regression analysis, age, SOFA score, CRP values, and vasopressor intake were found to be independent risk factors for mortality, whereas high-dose vitamin C intake was associated with risk reduction mortality. In multivariate regression analysis, age and high CRP values were associated with mortality. The mortality results of the patients were summarized in Table 2, Table 3, and in Figure 1. While the number of days with mechanical ventilation support was 11 in the control group during the follow-up, it was ten days in the study group, with no significant difference (p=0.921). There was no significant difference in terms of ICU stay. The median length of hospital stay was 15.0 (10.5-22.5) days in the control group and 23.5 (14.0-34.0) days in the study group (p=0.016). SOFA follow-up was evaluated every other day (0th, 2nd, 4th, and 6th days). It was observed that the SOFA score increased significantly in the control group compared to the study group (p=0.01). The daily variation of the SOFA score was shown in Table 4.

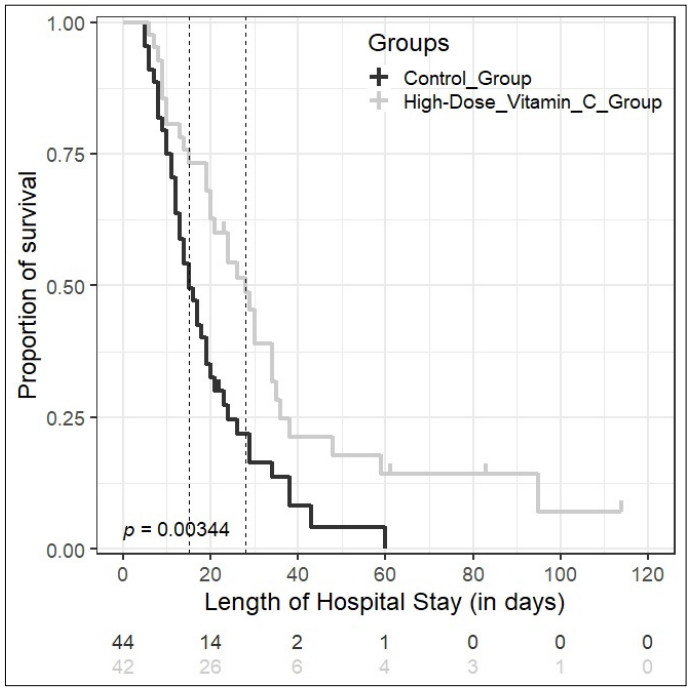

Figure 1.

Discussion

In our study, the efficacy of high-dose vitamin C in patients who were diagnosed with COVID-19 associated ARDS and were invasive mechanically ventilated in the ICU was analyzed retrospectively. The baseline PaO_2/FiO_2 mean value of the patients included in the study was 128.27±58.69 and was an indicator of respiratory failure. In our study, positive effects of high-dose vitamin C on mortality were observed in this severe patient group. In the daily follow-up of the SOFA score, a relative improvement was detected in the vitamin C group compared to the control group as the days progressed. Here, the number of days of hospital stay was higher in the study group.

In our study, overall mortality was 82.6%. In another multicenter study, the mortality rate of COVID19 patients followed in the intensive care unit was 55.1%, while this rate was 80.6% in patients who were invasively ventilated (3). Considering that all patients included in our study were invasively ventilated, the two studies were similar in terms of mortality.

In the RECOVERY study, it was shown that the use of 6mg/day dexamethasone was associated with a decrease in 28-day mortality in patients requiring oxygen (12). The retrospective patient enrollment date in our study was prior to the publication of the RECOVERY study. Probably for this reason, none of the patients in the records had steroid use.

In the study conducted by Kavurgaci et al., among 323 patients hospitalized for COVID-19, high-dose vitamin C did not significantly affect mortality (13). In their study, only 7% of the patients were followed up in the ICU, affecting the mortality assessment. Moreover, a high dose of 2gr/day was accepted as a high dose by Kavurgaci et al. In our study, patients who took 200 mg/kg/day or more of vitamin C were included.

Table 4. The comparison of SOFA scores within and between study groups

SOFA score	Groups		Total (*n*=86)	*p*†
	Control (*n*=44)	High-Dose Vitamin C (*n*=42)		
Day 0	5.90±3.28[a]	7.79±2.63	6.85±3.10	**0.005**
Day 2	7.12±3.47[ab]	7.76±2.87	7.44±3.18	0.357
Day 4	8.11±3.13[b]	8.38±3.16	8.26±3.13	0.707
Day 6	8.97±3.10[c]	8.44±3.94	8.68±3.56	0.530
***p*‡**	**<0.001**	0.878	-	-

Values are expressed as mean±SD. Significant p values are shown in bold characters. Different superscripts in the same column indicate a statistically significant difference between groups.
p†: Between-group comparisons are performed using independent samples t test
p‡: Within-group comparisons are performed using one-way repeated measures analysis of variance

Our data showed that mortality was reduced in those who received high doses of vitamin C. Similarly, Gao et al. investigated a total of 76 invasively non-ventilated patients, and they found that a decreased mortality in COVID-19 patients who received high-dose vitamin C (14). In this study, a daily dose of 6 grams was accepted as high-dose vitamin C. In another study conducted with 60 patients using the same dose, no mortality difference was found (15). While a fixed dose of 6 g/day was used in these studies, patients in our study received vitamin C at doses of 200 mg/kg/day and above (minimum 12 gr/day-maximum 20 gr/day). In addition, since the study groups in these studies were patient groups who were not initially invasively ventilated, the expected mortality would be lower; therefore, it might be difficult to evaluate the effect of vitamin C on mortality alone.

According to our results, the daily increase in SOFA score was higher in the control group than in the study group. Similarly, Lv et al. evaluated a total of 117 sepsis patients (56 control, 61 vitamin c group), and observed a higher increment in SOFA score in the control group compared to patients who received high-dose vitamin C. In the same study, mortality was also significantly lower in the group that received vitamin C (16).

The need for RRT was less in the study group (36.4% in the control group and 14.3% in the study group p:0.019). Patients with chronic kidney failure and acute kidney failure were not included in our study, and this situation developed in the follow-up of patients who needed RRT. There is no comprehensive study examining the effects of high-dose vitamin C use on renal functions in COVID-19. Takigawa et al. showed that the use of high-dose vitamin C in mice reduced vancomycin-related nephrotoxicity and suggested that this might be due to the oxidative stress-reducing effect of vitamin C (17).

Limitations

Our study had some disadvantages. First, since the study design was retrospective, there was no one-to-one matching of patients regarding basic characteristics such as age, APACHE-II, and gender. In order to eliminate the limitation of this situation,

regression analyzes corrected for age, gender and APACHE-II score were performed. Second, it was impossible to standardize the non-vitamin C treatments (steroids, tocilizumab, etc.). Third, the use of the prone position was significantly higher in the study group; however, the fact that the use of the prone position was not associated with mortality in the regression analyzes reduces the limitation of this situation. The strength of our study is that this study is the first multi-center study which included only invasively ventilated COVID-19 associated ARDS patients.

Conclusion

In conclusion, ARDS associated with COVID-19 is a condition that causes high mortality. There are uncertainties about its treatment and an important part of the treatment is constituted by supportive treatments. As an adjunctive therapy in invasively ventilated patients with COVID-19-associated ARDS, high doses of vitamin C may reduce mortality and development of organ damage. Prospective, randomized controlled studies with larger numbers of patients are needed to confirm these findings.

AUTHOR CONTRIBUTIONS:

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References

1. Alexander EG, Susan CB, Ralph SB, et al.; Coronaviridae Study Group of the International Committee on Taxonomy of Viruses. The species Severe acute respiratory syndrome-related coronavirus: classifying 2019-nCoV and naming it SARS-CoV-2. Nat Microbiol. 2020;5:536–544. [CrossRef]
2. Cucinotta D, Vanelli M. WHO declares COVID-19 a pandemic. Acta Biomed. 2020;91:157–160. [CrossRef]
3. Gündoğan K, Akbudak İH, Hancı P, et al. Clinical outcomes and independent risk factors for 90-day mortality in critically ill patients with respiratory failure infected with SARS-CoV-2: a multicenter study in Turkish intensive care units [published correction appears in Balkan Med J. 2021;38:397. doi: 10.5152/balkanmedj.2021.20888]. Balkan Med J. 2021;38:296–303. [CrossRef]
4. Wang D, Hu B, Hu C, et al. Clinical characteristics of 138 hospitalized patients with 2019 novel coronavirus-infected pneumonia in Wuhan, China [published correction appears in JAMA. 2021;325:1113. doi: 10.1001/jama.2021.2336]. JAMA. 2020;323:1061–1069. [CrossRef]
5. Wu Z, McGoogan JM. Characteristics of and important lessons from the coronavirus disease 2019 (COVID-19) outbreak in China: summary of a report of 72,314 cases from the Chinese Center for Disease Control and Prevention. JAMA. 2020;323:1239–1242. [CrossRef]
6. Fisher BJ, Seropian IM, Kraskauskas D, et al. Ascorbic acid attenuates lipopolysaccharide-induced acute lung injury [published correction appears in Crit Care Med. 2011;39:2022]. Crit Care Med. 2011;39:1454–1460. [CrossRef]
7. Fowler AA 3rd, Syed AA, Knowlson S, et al. Phase I safety trial of intravenous ascorbic acid in patients with severe sepsis. J Transl Med. 2014;12:32. [CrossRef]
8. Carr AC, Maggini S. Vitamin C and immune function. Nutrients. 2017;9:1211. [CrossRef]
9. Fowler AA 3rd, 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 [published correction appears in JAMA. 2020;323:379. doi: 10.1001/jama.2019.21469]. JAMA. 2019;322:1261–1270. [CrossRef]
10. Collie JTB, Greaves RF, Jones OAH, et al. Vitamin C measurement in critical illness: challenges, methodologies and quality improvements. Clin Chem Lab Med. 2020;58:460–470. [CrossRef]
11. Hemilä H, Chalker E. Vitamin C can shorten the length of stay in the ICU. A meta-analysis. Nutrients. 2019;11:708. [CrossRef]
12. Horby P, Lim WS Emberson JR, et al; RECOVERY Collaborative Group. Dexamethasone in hospitalized patients with Covid-19. N Engl J Med. 2021;384:693–704. [CrossRef]
13. Kavurgacı S, Uzel Şener M, Yıldız M, et al. Effect of high-dose intravenous vitamin C on prognosis in patients with SARS-CoV-2 pneumonia [published online ahead of print, 2021 May 11]. Med Clin (Barc). 2021;S0025-7753(21)00252–9.
14. Gao D, Xu M, Wang G, et al. The efficiency and safety of high-dose vitamin C in patients with COVID-19: a retrospective cohort study. Aging (Albany NY). 2021;13:7020–7034. [CrossRef]
15. JamaliMoghadamSiahkali S, Zarezade B, Koolaji S, et al. Safety and effectiveness of high-dose vitamin C in patients with COVID-19: a randomized open-label clinical trial. Eur J Med Res. 2021;26:20. [CrossRef]
16. Lv S-J, Zhang G-H, Xia J-M, et al. Early use of high-dose vitamin C is beneficial in treatment of sepsis [Retraction Note: Early use of high-dose vitamin C is beneficial in treatment of sepsis. Ir J Med Sci. 2021;190:1183–1188. [CrossRef]
17. Takigawa M, Yatsu T, Takino Y, et al. High-Dose Vitamin C Preadministration Reduces Vancomycin-Associated Nephrotoxicity in Mice. J Nutr Sci Vitaminol (Tokyo). 2019;65:399–404. [CrossRef]