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The effect of high-dose vitamin C on renal functions in COVID-19 patients

Asu Özgültekin, Abdulhalim Karayel, Seher Yanatma, Osman Ekinci

University of Health Science Haydarpasa Numune Research and Training Hospital Department of Anesthesiology and Intensive Care, İstanbul, Turkey

ABSTRACT

Background: With its important properties, Vitamin C has been used in several diseases and sepsis. COVID-19 may cause sepsis, and therefore high dose Vitamin C has been integrated to the treatment protocols.Concerning the potential risk of oxalate nephropaty related with the use of long term or high dose Vitamin C, we retrospectively evaluated the COVID-19 patients treated with the high dose intravenous Vitamin C, in terms of kidney dysfunction.

Material and Method: Critically ill COVID-19 patients who were given Vitamin C 45-50 gr/day/5 days (Group C, n=21), and the ones who did not (Group NC, n=22) along with the hydroxychloroquine- favipiravir treatment were compared in terms of developing renal dysfunction within the 15 days of ICU stay.

Results: There were no difference in the development of renal dysfunction between the groups with and without Vitamin C treatment ($p>0.05$). But when the patients who had KDIGO stage 1 kidney damage on admission, and had worsening renal dysfunction during ICU stay were excluded, patients groups were more similar and the development of the renal failure was significantly more in Vitamin C group($p<0.05$).

Conclusion: We conclude that when administering high dose parenteral Vitamin C, kidney functions should be carefully assessed.

Keywords: COVID-19, Vitamin C, renal dysfunction, oxalate nephropaty

INTRODUCTION

Vitamin C is widely used in clinical practice due to its antioxidant features considering that it has protective effects against various oxidative stress related diseases such as arthritis, cancer, diabetes and ischemia. It has been shown that plasma vitamin C levels are generally low in intensive care unit (ICU) patients (1). On the other hand, it has been shown that vitamin C blood levels are inversely related to multiple organ failures and directly proportional to survival rates (2,3). The importance of high levels of vitamin C and parenteral replacement in critically ill patients has been emphasized (4). Vitamin C blood levels in critically ill patients with septic shock are low enough to suggest scurvy (5).

Due to these features of vitamin C, a treatment protocol with high doses of vitamin C, corticosteroid and thiamine has shown promising results in septic shock patients in the pre-COVID-19 period (1). Moreover, a number of similar studies using different doses of vitamin C, combinations and duration of treatment have been planned (6-12).

In literature, a number of studies have reported oxalate nephropathy due to accumulation of calcium oxalate crystals, acute tubular necrosis and acute renal failure after long-term use of vitamin C. Cases of renal dysfunction after short-term or single and high-dose administration of vitamin C have been reported (13-15).

In our study, we retrospectively evaluated the effects of high-dose vitamin C on renal functions in severe-critical COVID-19 patient groups requiring respiratory support treatment during the pandemic, in order to benefit from its strong antioxidant-high dose pro-oxidant effects.

MATERIAL AND METHOD

The study included a total of 44 patients who were diagnosed with severe (those requiring high flow nasal cannula-HFNC/ noninvasive mechanical ventilation-NIMV) or critical (those requiring invasive mechanical ventilation-IMV) COVID-19 and admitted to ICU for respiratory support, aged between 51 and 93 (72.46±11.26) years. The study was conducted between March and June 2020, after obtaining approval from the local ethics committee (HNEAH-KAEK 2020/KK/157) and Ministry of Health. The patients were divided into two groups. The first group (Group C, n=22) was consisted of the patients treated with Vitamin C, in addition to Hydroxychloroquine-Favipiravir treatment for five days. Patients who were treated and followed up with the same protocol but did not receive Vitamin C consisted the control group (Group NC, n=22).

Corresponding Author: Asu Özgültekin, asuozgultekin@yahoo.com

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In accordance with the hospital treatment protocols, patients were administered with 45-50 g/day (3*15 or 2*25 g) of vitamin C for an average of five days in COVID-19 ICU along with other treatment methods.

Due to the short duration of treatment and critical and serious condition of the patients, some stage 1 patients (1.5-1.9 times baseline) with acute kidney injury (AKI) based on Kidney Disease Improving Global Outcomes (KDIGO) criteria (16) have also been treated with vitamin C.

The demographic data of the patients, comorbidities, Sequential Organ Failure Assessment (SOFA) scores on the day of hospitalization, duration of Vitamin C administration, use of nephrotoxic drugs, changes in serum creatinine values based on KDIGO classification and the status of renal replacement therapy were evaluated from the patient records. Since Vitamin C administration was started with the hospitalization of the patients, the data analyzed covered the time period between the first and 15th days of follow up.

Statistical Analysis

The data of the study were analyzed using IBM SPSS Statistics 22 (IBM Corp. Released 2013. IBM SPSS Statistics for Windows, Version 22.0. Armonk, NY, USA). Shapiro Wilks test was used to analyze whether the data were normally distributed. Mann-Whitney U test was used to compare descriptive statistical methods (mean, standard deviation, frequency) and the non-normally distributed data for quantitative parameters. Fisher's Exact, Fisher Freeman Halton and Continuity (Yates) Correction tests were used to compare qualitative data. p <0.05 was accepted as statistical significance.

RESULTS

The study was completed with 43 patients (Group C, n=21 and Group NC, n=22). One patient in Group C who was treated with colistin more than three days had elevated creatinin levels.He was excluded from the study, as colistin-a nephrotoxic antibiotic was considered as a possible factor for renal dysfunction. The medical treatments, respiratory support and restrictive fluid therapy strategies in both groups were otherwise similar.

The patient characteristics, SOFA scores, comorbidities, presence of acute-chronic renal failure (ARF-CRF) at time of hospitalization and development of renal failure based on KDIGO criteria are summarized in **Table 1**.

The mean age of the patients in Group C was significantly lower than the mean age of the patients in Group NC (p=0.042). The rate of presence of ARF-CRF on admission in group C was significantly lower than Group NC (19 vs 59.1%) (p=0.018). There was no statistically significant difference between the groups in terms of the hemodiafiltration (HDF) rates and mean KDIGO staging (p> 0.05).

As the ARF-CRF rates in two groups were not equal, we performed a subgroup analysis that excluded some patients with stage 1 renal failure at the time of ICU admission, those the KDIGO staging was increased during the ICU stay, showing that the renal failure was worsening. Stage 1 renal failure in two patients in each group either improved or remained the same during the follow-up and treatment. These patients were not excluded from the study as we thought that these patients were not affected anyway (**Table 2**).

When the patient groups were equalized in terms of age and comorbidities, the frequency of renal dysfunction development in Group C was found to be significantly higher than the Group NC (57.9 vs.18.2%) (p=0.04). The KDIGO scores of the group that was not administered with vitamin C were significantly lower than the vitamin C administered group (p=0.037).

The all-cause ICU mortality rates of our study groups were high; Group C: 85.7%, Group NC: 81.9% (p>0.05). For the subgroups, the change in mortality rates was not significant either; Group C: 84.2%, Group NC: 63.6% (p>0.05). Vitamin C administration did not seem to have any beneficial effect in these severely ill COVID-19 patients.

Table 1: Patient characteristics and status of the patients

		Group C (n=21, %)	Group NC (n=22, %)	Total (n, %)	p
Gender					0.425[1]
	Male	14 (66.7)	11 (50)	25 (58.1)	
	Female	7 (33.3)	11 (50)	18 (41.9)	
Age Mean±SD (median)		69.19±11.11 (66)	75.59±10.72 (78.5)	72.46±11.26 (72)	0.042[4*]
Comorbidities Mean±SD (median)		0.86±1.01 (1)	1.18±1.05 (1)	1.02±1.03 (1)	0.277[4]
SOFA score Mean±SD (median)		6.14±3.18 (5)	7.0±4.20 (6)	6.58±3.72 (6)	0.607[4]
Severe/critical					1.000[2]
	Critical	18 (85.7)	18 (81.8)	36 (83.7)	
	Severe	3 (14.3)	4 (18.2)	7 (16.3)	
ARF-CRF	+	4 (19)	13 (59.1)	17 (39.5)	0.018[1*]
Development of ARF		12 (57.1)	13 (59.1)	25 (58.1)	1.000[1]
KDIGO					1.000[3]
	0	9 (42.9)	9 (40.9)	18 (41.9)	
	1	1 (4.8)	1 (4.5)	2 (4.7)	
	2	5 (23.8)	5 (22.7)	10 (23.3)	
	3	6 (28.6)	7 (31.8)	13 (30.2)	
KDIGO Mean±SD (median)		1.38±1.32 (2)	1.45±1.33 (2)	1.42±1.31 (2)	0.847[4]
HDF	+	3 (14.3)	5 (22.7)	8 (18.6)	0.698[2]

[1]Continuity (yates) correction, [2]Fisher's Exact Test, [3]Fisher Freeman Halton Test, [4]Mann Whitney U Test, *p<0.05; CRF: Chronic renal failure, ARF: Acute renal failure, HDF: Hemodiafiltration, KDIGO: Kidney Disease: Improving Global Outcomes, SOFA: Sequential Organ Failure Assessment,

Table 2: Subgroup analysis

		Group C (n=19, %)	Group NC (n=11, %)	Total (n, %)	p
Gender					0.2871
	Male	12 (63.2)	5 (45.5)	17 (56.7)	
	Female	7 (36.8)	6 (54.5)	13 (43.3)	
Age Mean±SD (median)		69.42±11.68 (66)	72.55±13.03 (71)	70.57±12.07 (70)	0.5613
Comorbidities Mean±SD (median)		0.79±0.92 (1)	1.55±1.04 (2)	1.07±1.01 (1)	0.0553
SOFA score Mean±SD (median)		5.95±3.14 (4)	4.73±2.8 (4)	5.5±3.03 (4)	0.2733
Severe/critical					0.3801
	Critical	16 (84.2)	8 (72.7)	24 (80)	
	Severe	3 (15.8)	3 (27.3)	6 (20)	
CRF-ARF	+	3 (15.8)	2 (18.2)	5 (16.7)	0.6191
Renal failure		11 (57.9)	2 (18.2)	13 (43.3)	0.0401*
KDIGO					0.0972
	0	8 (42.1)	9 (81.8)	17 (56.7)	
	1	1 (5.3)	1 (9.1)	2 (6.7)	
	2	5 (26.3)	0 (0)	5 (16.7)	
	3	5 (26.3)	1 (9.1)	6 (20)	
KDIGO Mean±SD (median)		1.37±1.3 (2)	0.36±0.92 (0)	1±1.26 (0)	0.0373*
HDF	+	2 (10.5)	0 (0)	2 (6.7)	

1Fisher's Exact Test, 2Fisher Freeman Halton Test, 3Mann Whitney U Test; CRF: Chronic renal failure, *p<0.05; ARF: Acute renal failure, HDF: Hemodiafiltration KDIGO: Kidney Disease: Improving Global Outcomes, SOFA: Sequential Organ Failure Assessment

DISCUSSION

COVID-19 is known to cause viral sepsis with cytokine storm triggering oxidative stress characterized by lung capillary endothelial activation, neutrophil infiltration and increase of reactive oxygen-nitrogen radicals. The absence of a treatment method that will neither prevent the development of viral infection nor cure the disease has brought options to reduce the cytokine storm-oxidant effects that increase the severity of the disease. Therefore, vitamin C has been added to treatment protocols first in in Wuhan, and then in various centers around the world. It has also been recommended for its strong antioxidant effects and the ability to use it in high doses in early terms of the disease (17-21).

Despite the fact that the disease can cause multiple organ failure and renal involvement up to 30% of the patients, as the oxalate nephropathy effect of Vitamin C appears mostly in long-term use, Vitamin C doses in COVID-19 for a strong and effective antioxidant effect seems to be high. Previous studies in sepsis also emphasize that large doses of intravenous Vitamin C should be used to prevent and manage oxidative stress (1,22,23).

In addition to the antioxidant effects of vitamin C, the pro-oxidant effects at very high doses are also discussed and it is emphasized that this effect will be more pronounced in very high doses. Vitamin C, as a pro-oxidant agent, may contribute to epithelial cell functions with its anti-inflammatory properties, while reducing pro-inflammatory mediator expression and alveolar damage (19). Reactive oxygen radicals, which emerge as a result of pro-oxidant effect, especially in the presence of metals such as free iron and copper, may also show antiviral effects. However, it has been reported that severe oxidative damage may also occur. Therefore, it has been stated that studies on dose optimization are required (24).

In our study, we aimed to assess the effect of very high dose (45-50 g/day) intravenous Vitamin C on renal functions in critically ill COVID-19 patients who were admitted to ICU during the pandemic. The patients who were administered with and without Vitamin C in addition to other medical treatment options were compared. Due to the high mortality of COVID-19 in critically ill patients, the duration of the study was kept short.

Although patients groups were similar otherwise, the mean age and the number of the patients who had acute-chronic renal failure during ICU admission were significantly different. Therefore we needed to perform a subgroup analysis, regarding these differences.

In order to distinguish whether the deterioration in kidney functions is related to intravenous and high dose administration of vitamin C treatment, it is necessary to eliminate other factors. However, this is not an easy task especially in severe COVID-19 patients with multiple organ failures. For example, in the control group that was not administered with vitamin C, there were 13 patients who had stage 1 renal failure, and one of them regressed to stage 0 and the other remained the same during the follow-up. However, in the same group, renal failure progressed to stage 2 and 3 in 11 patients. In this patient group, the patients were not treated with any kind of drugs that could affect kidney functions, and the fluid balance was closely monitored in accordance with the ICU protocols.

The factors which could cause fluid loss such as fever, gastrointestinal and respiratory losses, problems in feeding, as well as the findings on clinical examination at the time of hospitalization were evaluated based on the protocol used in COVID-19 patients, and restricted—controlled fluid therapy was started while monitoring to maintain the hemodynamics and urine output. The same fluid strategy was used in both groups.

When the patient groups were compared without excluding patients with stage 1 renal failure at ICU admission, we did not find any significant difference between the Vitamin C administered and not administered patient groups in terms of the number of patients who progressed to advanced stages based on the KDIGO criteria (Group C: 57.1% vs Group NC: 59.1%, p> 0.05) . However, when the above mentioned patients were excluded, the remaining patients-that is, stage 0 patients in both groups or those who regressed to stage 0 from stage 1 or those who were unaffected and remained as stage 1 (two patients in group C regressed from stage 1 to stage 0; one of the two patients in Group NC remained as stage 1 to and the other regressed from stage 1 to stage 0), the rates of patients with advanced KDIGO stages were 57.9% in group C and 18.2% in

Group NC ($p < 0.05$). This situation suggests that Vitamin C poses a risk for renal failure.

A number of sepsis studies have reported that 4-6 grams/day of vitamin C for five days is safe (1-12, 25, 26). Regarding the higher doses and COVID-19, there are some clinical trials conducted, but the results have not been published yet.

In a report investigating two severe cases of COVID-19, anuria has developed in patients on days 10 and 20 following 24 g/day of Vitamin C administration, with a total of 112 and 160 g of Vitamin C. Renal biopsy samples have shown accumulation of calcium oxalate crystals in both patients and it has been reported that the renal functions of the patients have improved after renal replacement treatments. It has been recommended that additional therapies to be used in COVID-19 treatment should be carefully selected based on the benefits and risks (27).

When high dose i.v vitamin C is administered, the metabolic conversion from ascorbic acid to oxalate increases. Since oxalate is normally excreted through the kidney, serum levels will increase in the presence of renal failure. Oxalate may accumulate in kidney and other tissues in patients with renal failure who are administered with mega-doses of vitamin C, therefore deterioration in kidney functions should be taken into consideration when using mega-dose vitamin C.

Thiamin, is recommended to use with vitamin C. In vitamin C metabolism, glyoxylate is an intermediate product. It is either reduced to oxalate, or oxidized to carbon dioxide in a reaction where thiamine diphosphate is a co-enzyme. Thiamine provides a protective effect against the conversion of vitamin C to oxalate (1,6-12).

During the pandemic period, while thiamine deficiency or septic shock was not always in question in COVID-19 patients, we used vitamin C alone, which was considered as a protective agent against a rapidly developing cytokine storm and a severe oxidant effect.

Despite the high doses and parenteral use, the short duration of use, the mild side effects, overcrowding of COVID-19 ICU and the tendency to try every medication that may have a potential benefit have pushed the physicians to ignore dose-dependent renal side-effects. Nevertheless, in this retrospective study, we saw that the patients who had stage 1 renal dysfunction were mostly chosen not to have high-dose vitamin C, therefore their number in control group were unequally high. In the last analysis where these patients were excluded from the study, the number of patients in this group decreased.

Among the patients included in the study with stage 1 renal failure, renal-replacement therapy was required in one of the two patients who was administered with Vitamin C. This patient had multiple comorbidities and a high SOFA score. Vitamin C was administered only for two days to this patient. However, a 58-year-old patient without any comorbidities who was administered with Vitamin C for nine days also received renal replacement therapy, but it is also very likely that this patient may have been effected due to rapid and severe progression of COVID-19. In addition, in the control group, the kidney functions of 11 out of 13 patients who were not administered with Vitamin C have deteriorated. This still suggests that the most important factor in COVID-19 patient group may be the comorbidities and the factors related to the disease.

In a large study conducted in the United States with 5449 patients, the rate of AKI associated with COVID-19 has been reported as 37% (31-47%), and 17% of all patients have required dialysis. About 1/3 of patients have been diagnosed with AKI at admission. In addition, it was found to be proportional to the severity of the disease, and it has been stated that 90% of the patients on mechanical ventilation have developed AKI. Age and comorbidity were found to be independent risk factors in development of AKI (28).

In our patient group, when both groups were evaluated together, renal damage at ICU admission was 38.6%, while this rate increased to 56.8% during the hospitalization in ICU. Considering that the majority of patients were critically ill and on mechanical ventilation, it can be discussed that COVID-19 may have caused this situation alone. However, when we compared the groups with stage 0 patients without any kidney injury, we can suggest that the clinically and statistically high rate of dysfunction development in the vitamin C group shows that the effect of mega-dose vitamin C cannot be ignored.

Even though the number of cases is low, we think that our study may be suggestive because it not only included only critically ill COVID-19 patients, but also the parenteral administration of vitamin C was far above the doses used to date. Up-to-date, studies using this dosage and method are generally case reports.

It should also be considered that no beneficial effect in terms of the outcomes could be shown in Vitamin C patient group. In the light of the current knowledge, staging of the disease and appropriate treatment options including Vitamin C according to the this seeming to have paramount importance.

CONCLUSION

To conclude, although we cannot show any additional concrete evidence such as renal biopsy in the active state of COVID-19, we believe that vitamin C should be cautiously administered as a pro-oxidant agent.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was conducted between March and June 2020, after obtaining approval from the local ethics committee (HNEAH-KAEK 2020/KK/157) and Ministry of Health.

Informed Consent: Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Referee Evaluation Process: Externally peer-reviewed.

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

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Author Contributions: All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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