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ORIGINAL RESEARCH

The use of IV vitamin C for patients with COVID-19: a case series

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ABSTRACT

Background: The coronavirus disease 2019 (COVID-19) pandemic has affected almost 2.5 million people worldwide with almost 170,000 deaths reported to date. So far, there is scarce evidence for the current treatment options available for COVID-19. Vitamin C has previously been used for treatment of severe sepsis and septic shock. We reviewed the feasibility of using vitamin C in the setting of COVID-19 in a series of patients.

Methods: We sequentially identified a series of patients who were requiring at least 30% of FiO2 or more who received IV vitamin C as part of the COVID-19 treatment and analyzed their demographic and clinical characteristics. We compared inflammatory markers pre and post treatment including D-dimer and ferritin.

Results: We identified a total of 17 patients who received IV vitamin C for COVID-19. The inpatient mortality rate in this series was 12% with 17.6% rates of intubation and mechanical ventilation. We noted a significant decrease in inflammatory markers, including ferritin and D-dimer, and a trend to decreasing FiO2 requirements, after vitamin C administration.

Conclusion: The use of IV vitamin C in patients with moderate to severe COVID-19 disease may be feasible.

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KEYWORDS
COVID-19; coronavirus; sepsis; vitamin C; mortality

1. Background

The coronavirus disease 2019 (COVID-19) pandemic has affected almost 2.5 million people worldwide with almost 170,000 deaths reported to date [1]. Patients present with a wide range of disease severity and certain comorbidities such as diabetes mellitus, hypertension, immunosuppression, and age have been associated with high morbidity and mortality [2]. There are no treatments with strong evidence of clinical benefit, and national and international guidelines recommend using experimental drugs as part of investigational trials [3–5]. There is growing evidence on the potential benefit of vitamin supplementation for prevention and treatment of viral infections, especially in vitamin-deficient population [6]. Vitamin C is essential for a normal and well-functional host defense mechanism, and pharmacological application of vitamin C is believed to enhance immune function [7]. Previous studies have shown that vitamin C inhibited replication of some viruses such as herpes simplex virus, poliovirus, and influenza [7]. There is potential utility in the use of vitamin C in viral infections and possibly COVID-19.

Here, we describe a small case series of patients with moderate to severe COVID-19 who received low to moderate doses of intravenous vitamin C in addition to common treatments for COVID-19.

2. Methods

We sequentially identified 17 patients confirmed to be Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) positive via single-test nasopharyngeal swab PCR who were requiring 30% or more fraction of inspired oxygen (FiO2) and who received IV vitamin C as part of the COVID-19 treatment. Patients were treated in the progressive care unit and medical intensive care unit of Albert Einstein Medical Center, Philadelphia, PA (USA). There was no age cutoff or exclusion criteria used. Patients were either on hydroxychloroquine, methylprednisolone, and/or tocilizumab as part of initial treatment for COVID-19. These were given regardless of vitamin C administration depending on the clinical prerogative of the treating physician. Doses of these medications were not standardized as there was no strong evidence for their use. Vitamin C was administered at a dose of 1 g every 8 h for 3 days. Baseline inflammatory markers such as D-dimer and ferritin were also obtained by chart review and compared before and after administration of the vitamin C regimen. Outcomes such as inpatient mortality and need for mechanical ventilation were also obtained. No formal ethical approval was secured as these medications were relatively safe and already part of the hospital formulary. Off label use of vitamin C however was subject to the usual informed patient consent citing the risks and potential unknown benefits. All patients received care based on the clinical decisions of treating physicians; formal ethical approval from hospital Institutional Review Board was not required.

2.1. Statistical analysis

Categorical data were summarized using frequency percentages. Continuous variables were presented as means. Paired T-tests were used to compare D dimer, Ferritin, and mean FiO2% pre and post vitamin C administration. Chi square was

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used to compare rates of inpatient mortality and need for mechanical ventilation among patients who took hydroxychloroquine, methylprednisolone, and tocilizumab.

3. Results

The mean age of patients in our series was 64 ± 14 years; 41% were females and the majority were African Americans (59%). Mean BMI (Body Mass Index) was 32.7, indicative of high prevalence of obesity. Hypertension and diabetes mellitus were present in 47%, while COPD and asthma in 24% of patients, respectively (see Table 1). The patients were started on vitamin C treatment at a median of 3 days (range 0–11 days) after hospital admission. This is approximately within a median of 8 days (range 3–18 days) after symptom onset. Out of 17 patients, 2 (12%) were treated in the medical intensive care unit (MICU) and 15 (88%) were treated in the progressive care unit (PCU). As initial treatment for COVID-19, patients received IV methylprednisolone with a dose range from 40 mg to 125 mg once to twice daily (total of 10/17 patients). Hydroxychloroquine was given at a dose of 400 mg twice daily for 1 day followed by 200 mg twice daily for 4 days (total of 14/17 patients); three patients had incomplete treatment not related to toxicity. Tocilizumab was given at a dose of 800 mg once for three patients; 800 mg twice for one patient and 600 mg once for two patients.

The inpatient mortality rate in this series was 12% with 17.6% rate of intubation and mechanical ventilation, respectively. On correlational analysis, only hypertension was significantly positively associated with need for mechanical ventilation ($r = 0.491$, $p = 0.045$), while age ($r = 0.508$, $p = 0.037$) and post treatment FiO2 requirements ($r = 0.700$, $p = 0.002$) were significantly positively associated with inpatient mortality. Analyses using paired T-tests showed significantly lower D-dimer and ferritin levels post treatment with vitamin C. FiO2 requirements also had a trend toward reduction but did not reach statistical significance (see Table 2). Further analyses of medications administered in combination with vitamin C showed no significant differences in terms of need for intubation and mortality among patients who received hydroxychloroquine, methylprednisolone, and/or tocilizumab. Of the three patients who needed intubation, one was on hydroxychloroquine and methylprednisolone, one was on methylprednisolone alone, and one was on hydroxychloroquine and tocilizumab. No adverse events directly related to the administration of vitamin C were recorded.

Table 1. Baseline Demographic and Clinical profile

Age (mean±SD)	63.82 ±14.20
Female gender	7 (41%)
BMI (mean±SD)	32.71±8.74
Race	
African American	10 (59%)
Caucasian	4 (23%)
Asian	1 (6%)
Hispanic	2 (12%)
Comorbidities	
COPD/asthma	4 (24%)
Heart Failure	2 (12%)
Diabetes	8 (47%)
ESRD	2 (12%)
Immunosuppression	1 (6%)
Coronary artery disease	4 (23%)
Hypertension	8 (47%)
Medications	
Hydroxychloroquine	14 (82%)
Methylprednisolone	10 (59%)
Tocilizumab	4 (23%)
Clinical outcomes	
Need for intubation	3 (17.6%)
In-patient mortality	2 (12%)

Table 2. Comparison of markers of disease severity pre and post treatment

	Pre-treatment	Post-treatment	p value
D-dimer	2169.29 ± 2425.21	1728.43 ± 1341.28	p = 0.022
Ferritin	1392.07 ± 2031.62	1031.36 ± 974.84	p = 0.006
FiO2%	66.88 ± 25.59	47.06 ± 27.13	p = 0.186

4. Discussion

We present a case series of high-risk patients with advanced age and multiple comorbidities who tested positive for COVID-19 and were treated with IV vitamin C in addition to standard treatment for COVID-19. The patients had relatively high oxygen requirements with mean FiO2 of 67% ± 25% pre-treatment. In fact, hypertension was associated with the need for mechanical ventilation while age and post-treatment FiO2 requirements were significantly associated with inpatient mortality, which are all consistent with recent studies [2]. Median BMI was 32.7, indicative of high prevalence of obesity in our study population, which is an emerging risk factor for morbidity and severity of disease in COVID-19 [8].

Other organs and organ systems, such as the kidneys, remain a target for COVID-19, and many pathways have been proposed for its direct and indirect harmful effects [9]. Vitamin C together with corticosteroids and thiamine was found to be associated with reduced risk of progressive organ dysfunction, including acute kidney injury, and reduction in mortality in patients with severe sepsis and septic shock [10,11]. However, evidence seems to be conflicting as a recently published randomized trial found no significant clinical benefit [12]. Meanwhile, available literature describes how severe cases of COVID-19 tend to present with severe sepsis, ARDS, and cytokine storm [13]. Because of the septic shock and cytokine storm picture in severe COVID-19 disease, there are concerns for oxidative or free radical induced injury. Since the prevention and management of oxidative stress could be potentially achieved through large doses of antioxidants, this approach may be applicable to COVID-19 with administration of vitamin C [14]. Even though we did not collect data explicitly, further research could clarify the impact of vitamin C supplementation on renal function and development of renal injury.

Vitamin C is not the only vitamin shown to have potential benefit in viral infections and there are ongoing trials looking into the role of coadministration of vitamin D and vitamin C in treating mild to moderate COVID-19 [15]. Vitamin D deficiency has been associated with higher mortality in Europe and converging downstream pathways for SARS-CoV2 and vitamin D metabolism via angiotensin converting enzyme 2 (ACE 2) suggest a possible role for vitamin supplementation and modulation of immune response, especially in vitamin-deficient population [16,17].

In our series, we noted a significant decrease in inflammatory markers, including ferritin and D-dimer, and a trend to decreasing FiO2 requirements, although the latter was not statistically

significant. With a 12% mortality rate and 17.6% rate of need for mechanical ventilation, our results are relatively comparable to the recently published study of over 5000 patients showing 12% need for mechanical ventilation and 21% mortality rate [18]. Our patient series reflect a similar elderly age group with multiple comorbidities that are at high risk for poor outcomes in the setting of COVID-19. While the use of IV vitamin C might be safe and feasible in patients with COVID-19 with moderate to severe disease, we suspect that the effects on mortality and need for mechanical ventilation might be modest at best. Further randomized or controlled studies should aim to clarify the possible role of Vitamin C in severe COVID-19.

5. Conclusion

The use of IV vitamin C in patients with moderate to severe COVID-19 disease may be clinically feasible.

6. Limitations

This is a small case series of 17 patients with moderate to severe COVID-19 treated with IV vitamin C in addition to other medications currently being studied specifically for COVID-19, including hydroxychloroquine, corticosteroids, and tocilizumab. We cannot establish the true temporal effect of these medications due to the small sample size and lack of a control group. Some confounders including disease severity and natural course of disease should also be accounted for. The dose of vitamin C used in this study is low and treatment duration was short which is generally considered safe and inexpensive. We also cannot determine the extent of interaction of these medications with IV vitamin C and the possible effect of a higher dose of vitamin C. We also did not look at other inflammatory markers, such as C-reactive protein (CRP), lactate dehydrogenase (LDH), IL-6, or procalcitonin. We were also unable to take into consideration the use of other medications that may influence relevant outcomes, such as angiotensin converting enzyme (ACE) inhibitor agents.

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Declaration of interest

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