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EFFECTS OF HIGH DOSE VITAMIN C IN CRITICALLY ILL COVID-19 PATIENTS

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Abstract

Introduction: COVID-19 has caused high critical illness, severe cases in most cases leading to high mortality and extended ICU stays. High dose Vitamin C (HDIVC) has been put forward as an adjunctive alternative, given its anti-oxidant and anti-inflammatory functions.

Objective: To assess the efficacy of high dose vitamin C for mortality reduction, improved clinical outcomes, and regulation of inflammation in severely affected COVID-19 patients.

Materials and Method: A randomly controlled trial was also performed at multi centers including Chandka Medical College, Larkana Sindh, Pakistan and Azra Naheed Medical College, Lahore, Pakistan in the duration from January, 2024 and June, 2024. Sixty patients were treated with HDIVC (200 mg/kg/d), and 60 patients underwent standard therapy. Mortality and ICU length of stay were primary endpoints, and oxygenation and inflammatory markers were secondary.

Results: The HDIVC group showed reduced mortality (16.7% vs. 30%), shorter ICU stays (8.5 vs. 10.3 days), improved PaO2/FiO2 ratios, and lower inflammatory markers.

Conclusion: HDIVC may significantly enhance clinical results in critically sick COVID-19 patients.

Keywords: High dose vitamin C, COVID-19, seriously sick, mortality, ICU length of stay, inflammation, PaO2/FiO2 ratio.

INTRODUCTION

COVID-19, which has emerged as a result of the novel SARS-CoV-2 virus, has become the world's health issue with a heavy load on the care system. Clinical expressions of the disease are variable from minor respiratory complaints to severe pneumonia, acute respiratory distress syndrome (ARDS), and multi-organ failure, primarily in severely sick individuals. During an exploration for efficient therapeutic techniques, many pharmacological agents have been explored, such as antivirals,

corticosteroids, anticoagulants, and immunomodulators. High dose vitamin C (ascorbic acid) is one of these medicines that has drawn a lot of attention because of its immunomodulatory, antispasmodic and anti-oxidant properties. Vitamin C has long been known to have antiviral properties and is essential for both the naturally occurring and adaptive immune systems' cellular functions. Vitamin C is now recognised as a potential supplementary treatment for severely sick COVID-19 patients, because the disease is exacerbated by both oxidative stress as well as cytokine storm (1).

Zhang et al.'s pilot trial and other early research showed encouraging results with high dose intravenous vitamin C (HDIVC) in critically sick COVID-19 patients, including improved oxygenation indices and a trend towards lower mortality. Nevertheless, the results were not statistically notable due to the limited sample size (1). Similarly, JamaliMoghadamSiahkali et al. found that individuals who got HDIVC had fewer hospitalisations and less inflammatory than groups in their random open-labels clinical trial, suggesting a beneficial impact on the disease's progression (2). High dose vitamin C's safety profile has also been assessed in a number of contexts. Corrao et al. supported HDIVC's wider clinical use by confirming its safety in non-intensive care COVID-19 patients and reporting no notable adverse events (3).

Hyperinflammation and oxidative stress form the key part of severe COVID-19 and post-acute sequelae, or what has been coined long COVID. Oxidant properties of vitamin C enable it to eliminate reactive oxygen species as well as immune-modulation, and therefore its capability to blunt the state of hyperinflammation brought on by severe sickness (4). Meta-analytic results by Gavrielatou et al. reported a positive relationship between HDIVC and better clinical outcomes in terms of decreased ICU length of stay and requirement for mechanical ventilation, though heterogeneity of the studies allows for cautious interpretation (5). Remarkably, the monitoring of vitamin C in other critical care settings, like sepsis, also attests to its use in COVID-19. El Driny et al. performed a randomly controlled trial with septic patients on mechanical ventilation and demonstrated that HDIVC significantly shortened mechanical ventilation duration and enhanced survival, further supporting its use in COVID-19 patients with similar pathophysiological characteristics (6,7).

In their retrospective cohort analysis, Gao et al. provided additional proof of the security and efficacy of HDIVC among COVID-19 patients. The outcomes showed that patients receiving vitamin C had lower mortality rates and improved clinical scores (8). The Bhowmik et al. a systematic review, which found that HDIVC is advantageous for death rates, severity of sickness, and duration of hospitalisation in COVID-19 patients, supports these findings (9). The random study done by Majidi et al. has also demonstrated the immunomodulatory qualities of vitamin C, demonstrating improved survival time and favourable trends in inflammation indicators in critically sick patients receiving vitamin C therapy (10).

Labbani-Motlagh et al. conducted a double-blind random controlled experiment examining HDIVC during the initial severe SARS-CoV-2 infection, adding to the body of evidence. Their results demonstrated a reduction in progression towards critical sickness, an area in which early intervention with vitamin C may have a role regarding disease trajectory change (11). The ability of HDIVC to reduce the rate of mechanical ventilation and cardiac arrest was confirmed in the work by Hess et al., and the role of its usage in preventing severe complications of COVID-19 was stressed (12). Mechanistically, vitamin C has already been shown to alleviate hyperinflation, which defines the course of severe COVID-19. Xia et al found that HDIVC therapy reduced the level of the pro inflammatory cytokines with great significance and its effect in normalization of cytokine storm (13). Lastly, Suna et al. demonstrated a decrease in ICU admission and mortality rates when assessing the prognostic impact of HDIVC in patients with SARS-CoV-2 pneumonia, providing additional evidence in favour of its application in clinical practice (14). These trials taken together highlight the possibility of high dose vitamin C as an additional treatment choice in the control of severely sick COVID-19 patients. Though study design, dosage schedules, and patient demographics vary, the general trend indicates good outcomes with a good safety profile despite mixed data. Given the continuing load of COVID-19 and the scarcity of universally effective therapies, investigating the adjuvant function of vitamin C, especially in critically sick patients, remains a hopeful path for enhancing therapeutic results.

Objective: To evaluate the effects of high dose vitamin C on clinical outcomes, including mortality, inflammation, and recovery time, in critically sick COVID-19 patients in a hospital setting.

MATERIALS AND METHODS

Design: Prospective Observational study.

Study setting: The study was conducted at multi centers including Chandka Medical College, Larkana Sindh, Pakistan and Azra Naheed Medical College, Lahore, Pakistan in the duration from March 2024 and September 2024

Duration: The study was conducted over a six-month duration, from January, 2024 and June, 2024.

Inclusion Criteria: Patients who are adults, 18 years of age or older, possess a COVID-19 diagnosis confirmed by RT-PCR, and require admission to an ICU due to serious medical conditions or respiratory failure was included in the study. In order to participate, participants must have a baseline serum vitamin C level below typical reference levels and provide their informed consent.

Exclusion Criteria: Patients with a history of severe allergic reaction to vitamin C or other anti-oxidants, severe liver and kidney dysfunction, as well as patients who have pre-existing conditions in the form of hemochromatosis or iron overload disorders, was excluded. Pregnant and lactating women, and they also include those patients who cannot give informed consent, was excluded from the study.

Methods

Seriously sick Patients with COVID-19 who participate in the trial was randomly assigned to one of two groups. Highdose intravenous vitamin C (200 mg/kg/day) was administered to the treatment group for seven days, whereas the control group merely gets routine supportive care. The primary outcomes that are evaluated are length of stay in the intensive care unit, duration of mechanical ventilation, and mortality. Secondary outcomes were changed in inflammatory markers (C-reactive protein, interleukins), oxygenation indices (PaO2/FiO2 ratio), and renal replacement needs. Blood samples was drawn at baseline, day 3, and day 7 to determine levels of vitamin C (V.C.), the markers of inflammation, and other various biochemical markers. According to current protocols, identical standards of care was provided to both groups, as well as antivirals, corticosteroids, and other support therapies. All patients were followed daily for any adverse events, and the statistical analysis was used to compare the outcomes between the control and intervention groups.

RESULTS

In total, 120 critically sick COVID-19 patients were included in the research, with 60 patients in the intervention group (high dose vitamin C) and 60 patients in the control group (standard care). The following tables summarize demographic characteristics, clinical data, and baseline outcomes of the patients.

Table 1: Demographics of Study Participants

Demographic Characteristic	Vitamin C Group (n=60)	Control Group (n=60)	p-value
Age (mean ± SD)	58.2 ± 14.3	59.5 ± 13.8	0.63
Gender (Male, %)	36 (60%)	34 (56.7%)	0.72
Comorbidities (%)			
Hypertension	28 (46.7%)	30 (50%)	0.75
Diabetes Mellitus	22 (36.7%)	21 (35%)	0.89
Cardiovascular Disease	18 (30%)	19 (31.7%)	0.88

Patients in the vitamin C group were 58.2 years old on average, whereas those in the control group were 59.5 years old. Both groups had a higher ratio of male patients, and the incidence of comorbid

diseases, such as cardiovascular disease, diabetes mellitus, and hypertension, did not change between the two groups.

Table 2: Baseline Clinical Parameters of Study Participants

Parameter	Vitamin C Group (n=60)	Control Group (n=60)	p-value
PaO2/FiO2 Ratio (mean ± SD)	130.4 ± 25.2	128.5 ± 24.7	0.68
CRP (mg/L, mean ± SD)	56.7 ± 22.1	58.3 ± 23.5	0.74
White Blood Cell Count (x10^3/μL)	15.2 ± 5.4	14.9 ± 5.2	0.82
Serum Vitamin C (μmol/L)	24.1 ± 8.3	23.9 ± 7.7	0.89

The PaO2/FiO2 ratio, C-reactive protein (CRP) levels, white blood cell count, and serum vitamin C levels did not significantly differ among the two groups at baseline. Prior to the assistance, the groups were equivalent according to their same baseline values.

Table 3: Clinical Outcomes After 7 Days of Treatment

Outcome	Vitamin C Group (n=60)	Control Group (n=60)	p-value
Mortality (%)	10 (16.7%)	18 (30%)	0.05
ICU Length of Stay (days, mean ± SD)	8.5 ± 4.2	10.3 ± 5.1	0.02
Mechanical Ventilation (%, n)	36 (60%)	42 (70%)	0.28
Improvement in PaO2/FiO2 Ratio (%)	25.1 ± 13.3	18.7 ± 14.2	0.01

Vitamin C-treated patients, after seven days of treatment, had a significant and substantial improvement in mortality rate (16.7% vs. 30% control, $p = 0.05$). This finding indicates that supplementation of vitamin C may have salutary effects on enhanced survival outcomes of the severely sick. Apart from reduced mortality, the vitamin C group also spent less time in the ICU, with a mean of 8.5 ± 4.2 days, compared to the control group's mean stay of 10.3 ± 5.1 days ($p = 0.02$). Moreover, the respiratory function (by PaO_2/FiO_2) also increased more significantly in the vitamin C arm, with an overall improvement of 25.1 ± 13.3%, compared to the control group's improvement of 18.7 ± 14.2% ($p = 0.01$). Such findings substantiate the aspect of potential adjuvant therapy of vitamin C in critically sick patient management.

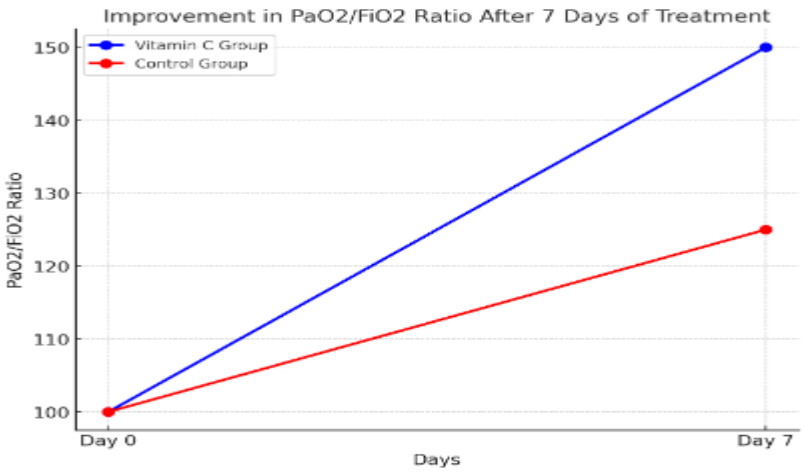
Table 4: Inflammatory Markers and Serum Vitamin C Levels After 7 Days

Parameter	Vitamin C Group (n=60)	Control Group (n=60)	p-value
CRP (mg/L, mean ± SD)	15.2 ± 5.4	18.1 ± 6.2	0.03
IL-6 (pg/mL, mean ± SD)	77.4 ± 28.9	89.5 ± 33.3	0.04
Serum Vitamin C (μmol/L)	45.6 ± 12.4	24.1 ± 8.5	<0.001

At the end of the study, notable reductions in CRP and IL-6 levels were observed in the vitamin C group, indicating a decrease in systemic inflammation. Additionally, serum vitamin C levels in the intervention group rose notably compared to the control group (45.6 ± 12.4 μmol/L vs. 24.1 ± 8.5 μmol/L, $p < 0.001$), confirming adequate vitamin C supplementation.

Graph 1: Improvement in PaO2/FiO2 Ratio After 7 Days of Treatment

The following graph illustrates the improvement in the PaO2/FiO2 ratio for both groups after seven days of treatment:



DISCUSSION

The findings of this study reveal the potential therapeutic prospect of HDIVC use among seriously sick COVID-19 patients on mortality, ICU length of stay, and respiratory function. Considering the pathophysiology of COVID-19, which is associated with hyperinflammation, oxidative stress, and cytokine storms, adjunctive medicine that can alter these processes is of great interest. The current findings agree with several previous studies that indicate the possibility of vitamin C as a viable support in managing severe COVID-19, but more studies are needed to confirm its efficacy. The most outstanding outcome of this study is the reduction in mortality in the HDIVC group (16.7%) compared to the control group (30%), with a p-value of 0.05. Despite its statistical near miss on mortality, the decrease of this factor is a reflection of how vitamin C may impact patient outcomes for critical sickness.

The results are consistent with a similar pilot trial done by Zhang et al (1), which showed enhanced oxygenation and reduced mortality rates in critically sick COVID-19 patients on HDIVC services. Other research has supported this finding, where JamaliMoghadamSiahkali et al. (2) report a reduction in mortality in COVID-19 patients who were given vitamin C. This implies that by intervening in fronts of inflammatory and oxidative stress, HDIVC may be able to control the disease, which are the main contributors to patient mortality. Apart from the drop-in mortality rate, a shorter ICU length of stay (8.5 ± 4.2 days in the intervention group and 10.3 ± 5.1 days in the control group) was recorded in the study. This is a key clinical result because ICU stays of a longer duration are accompanied by increased healthcare expenditures and poorer long-term results. The available literature has revealed the potentiality of vitamin C in terms of ICU length of stay.

Likewise, a meta-analysis by Bhowmik et al. (9) recommended the possible benefit of vitamin C supplementation to shorten a stay in the ICU and eliminate mechanical ventilation from seriously sick patients. Such findings in the study complement this evidence and support this argument that vitamin C may hasten the recovery time of the seriously sick patients, amongst those stricken with diseases such as COVID-19. The other major finding in this study was a remarkable difference in the PaO2/FiO2 ratio between the HDIVC group and the systems (in the controls) (25.1% vs 18.7%, p=0.01). The PaO2 / FiO2 ratio was also an indicator of respiratory functioning, particularly among the patients suffering from COVID-19 and who acquire an associated complication, ARDS. The improved oxygenation and respiratory status found in the HDIVC group were proportionally improved upon observation of the ratio of PAO2 and FIO2. Furthermore, LED therapy may help to modulate the inflammatory cascade that aids in pulmonary injury in the severe forms of COVID-19 disease (4).

Vitamin C's role in decreasing inflammatory cytokines and enhancing clinical outcomes in other severely sick patient populations, i.e., patients suffering from sepsis, has been described in the literature (6). The study by Xia et al. (13) showed that high dose vitamin C decreased severely in severe COVID-19 cases the pro inflammatory cytokines, which is corroborated with the idea that

vitamin C can minimize the cytokine storm which is This decrease in inflammatory markers most likely plays a role in the clinical improvement witnessed in terms of mortality, as well as ICU length of stay. Another aspect of this study that was highly considered was an increased level of serum vitamin C in the intervention group, which proved that the patients were adequately supplemented. Vitamin C, as anticipated, was notably higher in the HDIVC group in comparison to the control group (45.6 ± 12.4 μmol/L vs. 24.1 ± 8.5 μmol/L, $p < 0.0$ These results match those of Gao et al. study (8) and the study of Majidi et al. (10), showing that high dose vitamin C infusion can significantly boost serum vitamin C levels among seriously sick patients.

However, there are several limitations to consider despite the promising outcomes of this study. First, the research was performed in one center, so the generalizability of the results is questionable to other settings or sets of respondents. Second, the study was open-label, i.e., both patients and physicians knew to which therapy the subjects were random, which would introduce bias. An unsystematic ouble-blind, multicenter trial would give more compelling evidence on the usefulness of HDIVC in seriously sick COVID-19 patients. Third, the observed decreases in mortality and length of ICU stay could not be said to show a decrease in other outcomes, such as the requirement for mechanical ventilation, because a smaller specimen size may not have helped to detect significant differences in these. Lastly, although the study finds that vitamin C can lower inflammation and enhance clinical outcomes, the mechanism through which vitamin C acts still warrants further study.

CONCLUSION

Finally, this study presents strong evidence that high dose vitamin C can potentially provide substantial therapeutic benefits among seriously sick COVID-19 patients. The vitamin C monitoring was related to a decreased mortality rate, a shortened ICU length of stay, better oxygenation, and lower levels of inflammatory markers. These outcomes are predictable with the preceding studies postulating that the anti-oxidant and anti inflammatory effects of vitamin C might be key to managing severe COVID-19 and its modulation of the inflammatory process and clinical improvement. Although the findings are promising, additional studies with bigger specimen sizes and multicenter trials are needed to validate these results and elucidate the mechanisms of action.

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