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EFFECTS OF MEGA DOSE VITAMIN C IN CRITICALLY ILL COVID-19 PATIENTS: A RANDOMIZED CONTROL TRIAL

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Abstract: *Severe acute respiratory coronavirus 2 (SARS-CoV-2), COVID-19, caused a pandemic that took millions of lives worldwide. The main reason is a lack of preparedness and knowledge about the treatment options. With the advancement in the understanding of the SARS-CoV-2 virus, many treatment options have been analyzed that helped effectively to decrease the mortality caused by this virus. Vitamin C is known to boost immunity and slow down the progression of viral infection. The current study was designed to assess the effectiveness of a high dose of intravenous (IV) vitamin C in COVID-19 infection. The clinical trial registered on 23/12/2020 at ClinicalTrials.gov (NCT04682574) was conducted in Bahria Town International Hospital, Lahore (BTIHL), Fatima Memorial Hospital, Lahore (FMH), and Evercare Hospital Lahore from 28/12/2020 to 10/4/2022. Two hundred seventy-eight critically ill patients with COVID-19 were categorized into two groups. One hundred thirty-nine patients were randomized in group VC (vitamin C), which was given a high dose (30 grams) of intravenous (IV) vitamin C for four days, whereas distilled water as a placebo was given to the control group (n=139) along with standard treatment protocols. All the patients were analyzed for primary outcomes in partial pressure of arterial oxygen (PaO2) to Fraction inspired oxygen (P/F) ratio and survival analysis. At the same time, levels of inflammatory and biochemical markers needed for intubation and length of hospital stay in both groups were compared as the study's secondary endpoint. Among the two groups, we did not find any differences in 28-day mortality (Log Rank P= 0.11). Similarly, no difference in the P/F ratio on the fourth day after the start of IV vitamin C treatment was noted (p=0.24). The median values of biochemical and inflammatory variables improved significantly in group VC on day 4. However, only hemoglobin levels remained non-significant between the groups. Mean days of hospital stay were slightly longer in group C. However, no statistical significance (p=0.941) was found. Although Group VC needed fewer intubations than Group C, results remained statistically insignificant (p= 0.273). This trial did not find any mortality benefit or improvement of the P/F ratio in critically ill patients. However, the VC group showed improvement in biochemical variables of prognostic importance, which seems to lower the chance of intubation and LOS in group VC. A further clinical trial with a large sample size is needed to reach the final conclusion.*

Keywords: COVID-19; P/F Ratio; Biochemical Variable; Mortality Benefits, Mega Dose Vitamin C

Introduction

COVID-19 infection caused by severe acute respiratory coronavirus 2 (SARS-CoV-2) has become a global problem that has cost millions of lives (Lai et al., 2020). It can present as asymptomatic mild, severe, or critically ill cases needing ICU admission (Jain et al., 2020). The critically ill patients admitted to the ICU had a high mortality rate due to septic shock, cardiovascular events, and sequential organ failure (Faqihi et al., 2020; Montrucchio et al., 2021). This high mortality is considered due to the activation of innate immune response and release of inflammatory and reactive oxygen species. This is

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known as cytokine storm (Goud et al., 2021). Therefore, it is considered that the worsening of symptoms after a few days is not only due to viral replication but potentiated by the activation of innate immune response and release of inflammatory biomarkers (Bartleson et al., 2021).

Considering this pathophysiology of COVID-19 infection, different treatment options were applied to decrease mortality. Vitamin C is one of the chief vitamins the body needs to synthesize collagen and combat oxidative radicals. It is conventionally considered the most potent element for ameliorating immunity (Boretti and Banik, 2020). Besides this, vitamin C plays a role in increasing carnitine, depleting histone methylation, and augmenting amidated peptides for hormonal regulation. Vitamin C assists phagocytic cells in chemotaxis and promotes bacterial killing. It is also involved in the apoptosis process and reduces tissue deterioration. A recent study conducted on COVID-19 patients showed that 94.4% of critically ill patients had undetectable levels of vitamin C (Chen et al., 2022).

Besides COVID-19 infection, patients with other critical illnesses showed hypovitaminosis. However, due to the limited absorption of vitamin C through the gut, its deficiency cannot be corrected orally. The preferable route is intravenous (IV) (Ran et al., 2020). It is proposed that supplementation with vitamin C can ward off systemic and respiratory infections. The recommended dose to combat prophylactic infections is 100-200 mg/d (Islam et al., 2021). however, the dosage for already infected patients is higher since metabolic needs are augmented (Marazuela et al., 2020). It is advised to take the dose daily because of the body's low storing capacity of water-soluble vitamins. The dosage varies for each disease surgery patient may require doses of more than 500 mg/day. In a study, an intervention on the mouse with Chediak- Higashi Syndrome improved chemotaxis by administering 200-500 mg/d vitamin C dose (Calder et al., 2020). The effect of vitamin C on humans having a common cold showed that it could reduce the duration of the condition. Two clinical trials demonstrated a positive effect in curing a common cold by administration of 6-8 g per day of vitamin C dose (Hemilä et al., 2021).

Furthermore, three randomized controlled trials proved that vitamin C can prevent pneumonia. Another study reported that vitamin C has a significant role in combating viral infections in upper respiratory tract infections. The use of antibiotics and vitamin C supplements represented satisfactory results in children below 6 years and those with an advanced stage of upper respiratory infection (URTI) (Vorilhon et al., 2019). Considering the potential role of vitamin C in confronting infection, its role was assessed in treating the novel COVID-19. It is proposed that only remdesivir is found to be an efficacious medication for treatment by FDA. Though, supplementation of minerals and vitamins can be a supportive therapy in managing COVID-19 patients. It is found that levels of vitamin C are decreased in patients in the initial stage of infection. The requirements rise because of metabolic needs. A high-dose IV injection can compensate for the depleting stores of Vitamin C in serum and leucocytes. This approach has revealed a curing effect in China and the US (Abobaker et al., 2020). Possibly, Vitamin C can produce an anti-inflammatory, antioxidant, immunomodulatory, and indirect antiviral effect in managing COVID-19. This study aimed to analyze the potential effect of a mega-dose of vitamin C in critically ill patients to reduce mortality and improve the P/F ratio as primary endpoints and assessment of inflammatory markers, length of hospital stays, and need for intubation between the groups as secondary endpoints.

Methodology

This is a multicenter, randomized control trial conducted in the ICU departments of three main hospitals in Lahore dealing with COVID-19 infection. 1. Bahria Town International Hospital Lahore (BTIHL) 2. Fatima Memorial Hospital (FMH), and 3. Evercare hospital. The distribution of cases and controls was 78/67, 34/42, and 27/30, respectively, in each hospital. The trial was approved by the hospital's institutional review board and ethical committee (IRBEC/BIH/09-2020) and registered on 23/12/2020 at ClinicalTrials.gov (ID: NCT04682574). This study included (N=278) both male and female critically ill COVID-19 patients confirmed on RT-PCR, and the severity of the disease was assessed according to the NHC of China that was released in the 7th edition of Diagnosis and Treatment Protocol for Novel Corna Virus. Thirty-five years were the lower, whereas 80 years were the upper age limit for inclusion criteria.

Patients with one of the following conditions were treated as critically ill. Having pneumonia, confirmed by chest imaging and admission to the ICU, Patients require assisted ventilation with oxygen saturation levels $\leq$ 93 at rest or O2 partial pressure/fraction of inspired oxygen (PaO2/FiO2) $\leq$ 300 mmHg. Patients with shock syndrome and multi-organ failure signs and symptoms need intensive care unit (ICU) monitoring and treatment. The patients who had an allergy to IV vitamin C on test dose or expired within 48 hours after the admission were excluded from the analyses. Informed written consent was taken before

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including the patients in the study. It is a Double-blind study in which the patients, doctors, and researchers did not know about their assigned group. The Block Randomization method randomized the patients into two groups, and the allocation ratio was 1:1. (Sealed Envelope Ltd. 2021). Create a blocked randomization list. [Online] Available from: https://www.sealedenvelope.com/simple-randomiser/v1/lists [Accessed 11 December 2020].

Intervention protocols: The group VC was given 10 gm of Vitamin C diluted in 100ml of distilled water for two hours, and this dose was repeated after 8 hours. In this way, the total dose of vitamin C given in 24 hours was 30 grams. This dose was given for 4 days. The placebo group was given 100ml distilled water without compromising the daily input/output balance. The solutions were prepared by the pharmacists, handed over to the ICU in-charge nurse, and infused under the supervision of the doctors on duty. The nurse in charge noted any adverse event vigilantly and was ready to deal with any emergency.

Standard treatment protocols: The standard treatment protocol was given in both groups according to international guidelines. This treatment protocol included remdesivir, corticosteroid, low molecular weight heparin, and antibiotics. We did not include patients who received tocilizumab in our study.

Data collection: Demographic data, including gender, age, and BMI, were obtained in all groups and transferred to the Excel sheets for further analysis. The comorbid conditions were also noted and compared in both groups to analyze the confounding status of the data. The P/F ratio was determined by measuring PaO2 from the atrial blood gases analyses (ABGs) and FiO2 from the oxygen supplementation method. We compared the P/F ratio on the 1st and 4th day from the start of the Mega-dose of Vitamin C. All the patients were followed for 28 days, and those who expired before completing the 28th day were given the value of 1. The biochemical variable was noted and compared in both groups on the days 1st and 4th. The Glasgow coma scale was used to assess the conscious status of the patients, where 3 was the minimum score (unconscious), and 15 was the maximum score (conscious). Based on biochemical analyses, lowest mean arterial pressure (MAP), peak temperature, electrolytes, and GCS scale, the Acute Physiology and Chronic Health Evaluation II (APACHE II) score was also measured. The total length of hospital stay in both groups was also measured and compared between the groups. As a secondary outcome, we also compared the number of patients who needed invasive oxygen (ventilatory support) in both groups.

Statistical analysis: Continuous variables were represented as mean and standard deviation or by the median and interquartile range (IQR). They were compared by t-test or Mann-Whitney U test. Categorical data were represented as frequency and compared by using the chi-square test. To measure the 28 days of survival, Kaplan-Meier analyses were used. 1 was the output variable, and 0 was considered 28 days of survival. The Log-Rank test compared survival curves; p-values less than 0.05 were statistically significant.

Results

A total of 308 participants were analyzed during this analysis. Thirty participants dropped out because of the volition of the inclusion criteria (Figure 1.). The distribution of participants in three hospitals is summarized in Figure 2. 53.6% of participants were male, and the mean age of group VC was comparable with group C (58.7 ±11.9 vs. 57.6 ±12.7, respectively, with P= 0.475). The body mass index (BMI) also showed an insignificant difference between the groups (p= 0.853). The most common comorbid conditions in our study was Hypertension (34.5%) and Diabetes (21.2%), followed by asthma and chronic obstructive pulmonary disease (COPD). (Table 1)

Primary outcomes: During the 28 days total of 16 (5.8%) patients expired after 24 hours, of which 11(7.9%) were in group C and 5 (3.6%) were in group VC. The 28-day mortality was estimated using the Kaplan-Meier analysis, and the survival curve was compared by log-rank test (p=0.11), which showed no significant difference in survival between the two groups infected by COVID-19 infection (Figure 3). Similarly, we did not find a significant difference in the final P/F ratio between the groups (Figure 4).

Secondary outcome: The study's secondary endpoints were to assess the biochemical markers of prognostic importance and clinical outcomes in both groups. TLC, Neutrophils, Lymphocytes, D. dimer, CRP, procalcitonin, LDH, and Ferritin levels on the 4th day were compared, showing a significant difference in both groups on the 4th day. The VC group showed improvement or less deterioration in these hematological and inflammatory biomarkers than the Control group. Only hemoglobin levels were found not significantly changed on the 4th day (Table-2). We also found less need for intubation in the VC group compared to the control group but not statistically significant (3.6% vs. 6.5% respectively, p=.273). Similarly, the APACHE-II score was not improved between the groups on day 4 (p=0.42).

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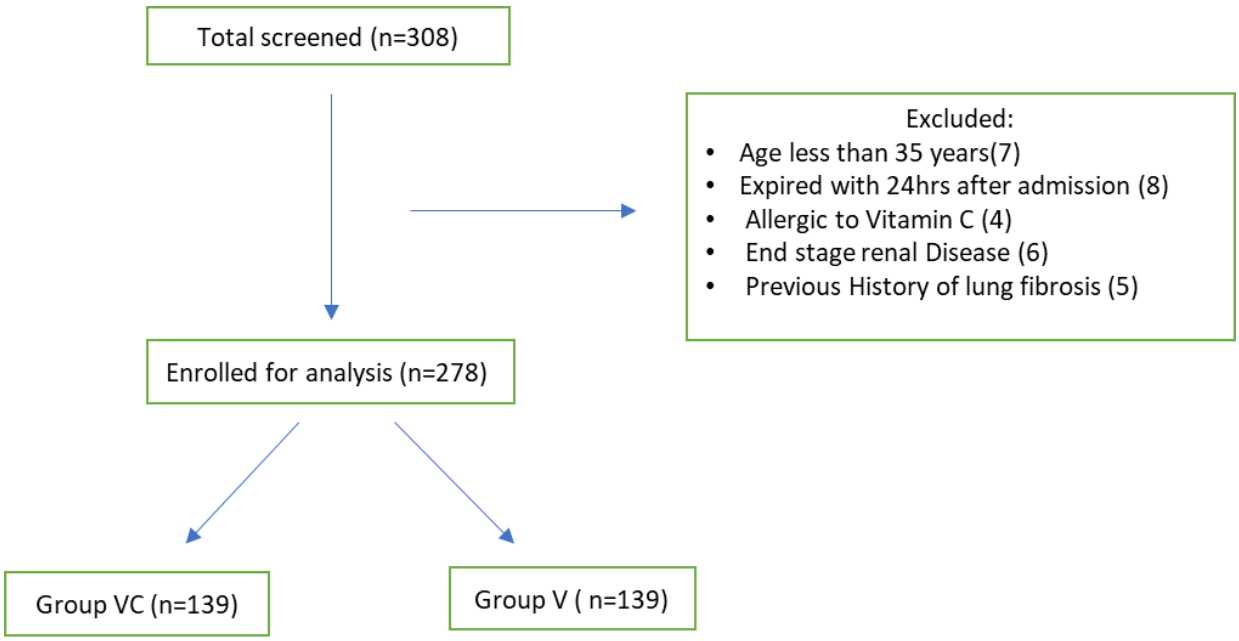

Figure-1: *The chart showed that the out of 308 participants, 30 were excluded, and the rest of the 278 participants who met the inclusion criteria were divided into two groups.*

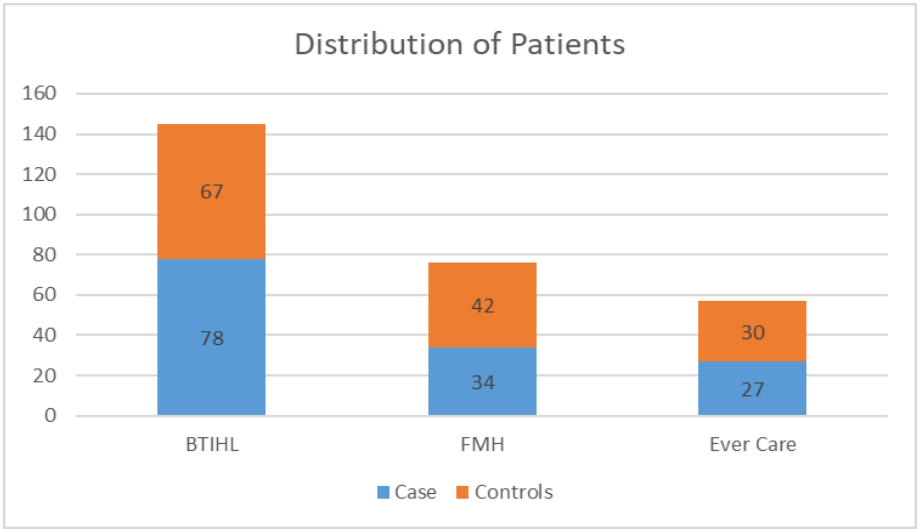

Figure-2: Distribution of cases and controls in three hospitals in Lahore
(BTIHL: Bahria town international Hospital Lahore, FMH: Fatima memorial hospital Lahore)

Table-1 Baseline Characteristics and comorbid conditions:

Variables	Construct	Vitamin C	Control	Total	P-value
Gender	Male	73 (48.9%)	76 (51.1%)	149 (53.6 %)	0.401
	female	66 (51.2%)	63 (48.8%)	129 (46.4%)	
Age (Years)		58.7 ±11.9	57.6 ±12.7		0.475
BMI (kg/m^2)		30.78[28.33-32.94]	30.85[29.29-2.30]		0.853*
P/F ratio	Day 1	183 [88.00-284.00]	135[84-219]		0.443*
APACHE II	Day 1	14.5[10.4–16.9]	15.0 [11.5–16.5]		0.411*

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Comorbid conditions					
HTN	No	94 (67.6%)	88 (63.3%)	182 (65.5%)	.449
	Yes	45 (32.4%)	5136.7%	96 (34.5%)	
DM	No	112 (80.6%)	107 (77.0%)	219 (78.8%)	.463
	Yes	27 (19.4%)	32 (23.0%)	59 (21.2%)	
Asthmatic	No	108 (77.7%)	114 (82.0%)	222 (79.9%)	.370
	Yes	31 (22.3%)	25 (18.0%)	56 (20.1%)	
COPD	No	117 (84.2%)	109 (78.4%)	226 (81.3%)	.219
	Yes	22 (15.8%)	30 (21.6%)	52 (18.7%)	
IHD	No	114 (82.0%)	113 (81.3%)	227 (81.7%)	.877
	Yes	25 (18.0%)	26 (18.7%)	51 (18.3%)	
Renal Dysfunction	No	133 (95.7%)	135 (97.1%)	268 (96.4%)	.519
	Yes	6 (4.3%)	4 (2.9%)	10 (3.6%)	
Deaths	No	134 (96.4%)	128 (92.1%)	262 (94.2%)	.122
	Yes	5 (3.6%)	11 (7.9%)	16 (5.8%)	
Intubation	No	134 (96.4%)	130 (93.5%)	264 (95.0%)	.273
	Yes	5 (3.6%)	9 (6.5%)	14 (5.0%)	

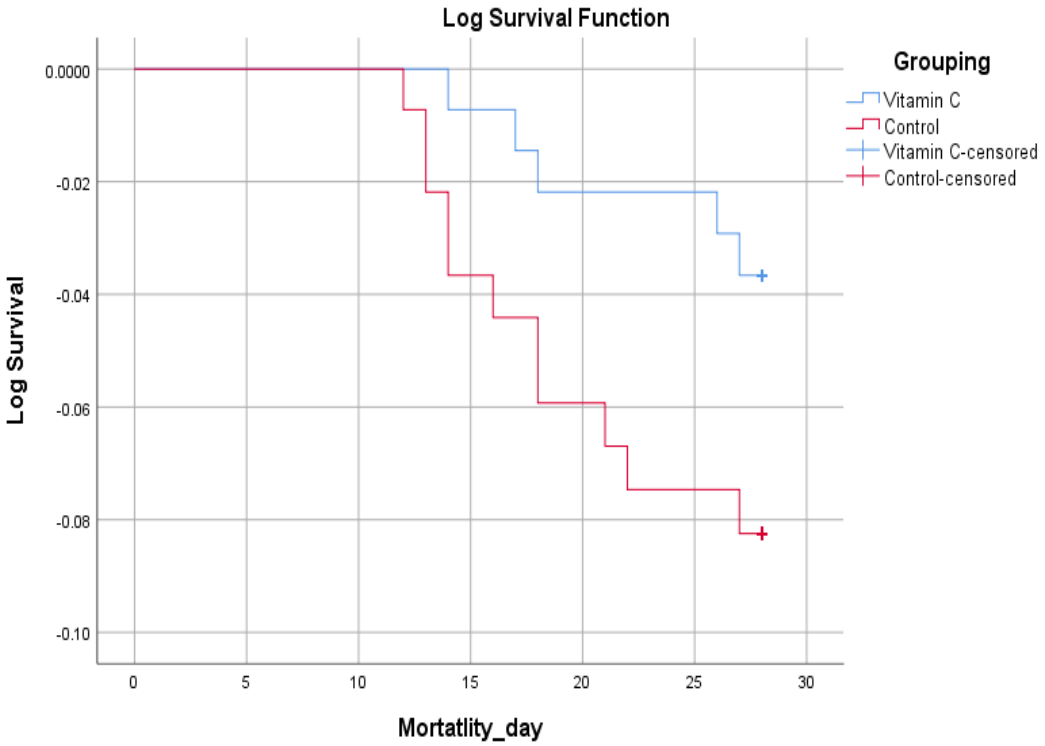

Figure-3: 28 days mortality from the start for a mega dose of Vitamin C (day 1) was measured by Kaplan-Meier analysis. Survival curves were compared by log-rank test (p= 0.11)

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Table-2 Comparison of hematological and inflammatory biomarkers

Variables	Days	Group VC		Group C		P-value
		Median	IQR	Median	IQR	
Hemoglobin (g/dl)	1	11.44	10.21-12.40	11.02	9.88-12.85	0.68
	4	11.68	10.67-12.70	11.36	10.77-12.25	0.88
TLC (10^9/L)	1	10.65	8.64-11.60	10.34	8.99-12.01	0.09
	4	9.38	7.59-10.69	11.02	9.21-12.80	0.00
Platelets ($10^3/\mu l$)	1	206	162-254	198	158-255	0.11
	4	190	167-228	170	156-190	0.00
Neutrophils (%)	1	80	72-83	81	77-85	0.32
	4	77	70-87	89	73-102	0.00
Lymphocytes (%)	1	32	24-38	36	23-41	0.06
	4	25	14-33	12	6-21	0.00
Bilirubin (mg/dl)	1	1.10	0.81-1.42	1.06	0.74-1.32	0.35
	4	1.14	0.68-1.44	1.39	1.00-2.06	0.00
Creatinine (mg/dl)	1	0.4	0.21-0.56	0.6	0.4-1.0	0.21
	4	0.81	0.53-1.27	1.75	1.12-2.44	0.00
CRP (mg/dl)	1	16.6	14.6-19.2	14.2	9.2-18.4	0.09
	4	6.54	5.11-7.85	28.93	25.84-31.37	0.00
D. Dimer (ng/dl)	1	189.6	146.3-222.1	204.6	149.6-265.6	0.65
	4	141.42	88.00-188.06	300.87	260.14-388.29	0.00
Ferritin (ng/dl)	1	906.52	552.65-1203.55	1001.50	602.52-1400.65	0.06
	4	830.60	411.95-1103.57	1794.75	1081.40-2307.39	0.00
LDH (U/L)	1	306.21	251.65-380.62	312.58	244.69-391.2	088
	4	323.44	231.18-386.39	386.26	268.88-471.45	0.00
PCT (ng/ml)	1	1.12	0.89-1.42	1.21	0.95-1.39	0.32
	4	1.46	0.94-1.89	2.18	1.46-2.77	0.00
APACHE II score	4	15.0	11.5–16.5	12.4	9.0–14.0	0.42

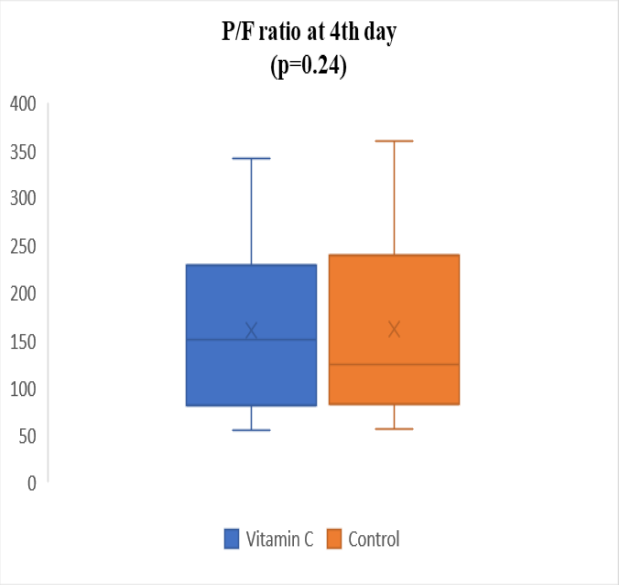

Figure-4: Difference of P/F ratio measured on day 4 after the start of Vit C (I.V)

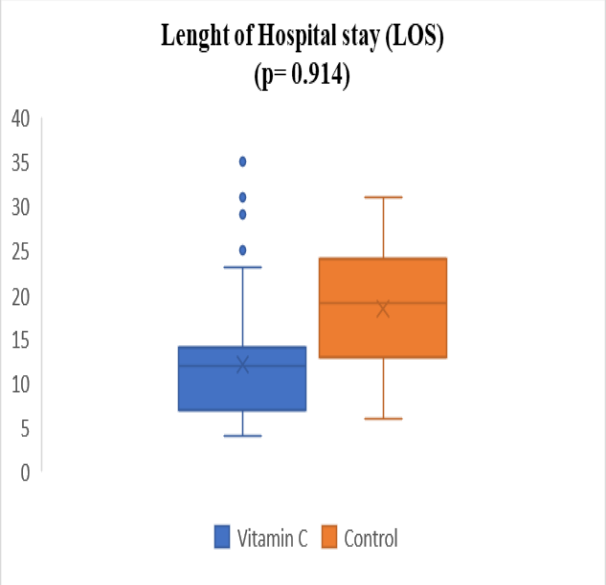

Figure-5 shows differences in the length of hospital stay between the two groups.

At last, the mega dose of vitamin C did not show any effect in shortening the length of hospital stay in patients of critically ill COVID-19 patients (Figure 5).

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Discussion

The existing literature suggests that vitamin C can be an effective supporting element in managing infections and respiratory diseases(Boretti and Banik, 2020; Calder et al., 2020). In this randomized control trial, 30 grams of vitamin C was administered for 3 days to critically ill COVID-19 patients to assess its effectiveness. In a previous study, the dose of 12 gm per day was beneficial in acute respiratory distress syndrome (ARDS) and patients with sepsis. High doses of vitamin C have also been used in malignancies [16]. The NIH reported a daily 1.5 g/kg body weight of IV vitamin C as a safe dose (Cheng, 2020). Therefore, our 30 grams daily dose is safe and expected to benefit patients with COVID-19. Vitamin C is important in inhibiting nuclear factor Kappa-B (NFκB), a pro-inflammatory cytokine. In this way, it acts as a potent immune modulator and inhibitor of inflammatory response (Chu et al., 2016). The alveolar endothelial cells injury led to hypoxia and acute respiratory distress syndrome due to the activation of the inflammatory biomarkers (Matthay et al., 2019). Hence, the VC should improve the P/F ratio in COVID-19 patients by protecting the respiratory membrane. Our study showed no significant improvement in the P/F ratio in critically ill patients in Group VC compared to the placebo group. These results contradict the study's results in which the delta mean difference on day 7 showed improvement in the P/F ratio in the high dose (24 grams/day) IV vitamin C group.

The survival analysis in our study also showed no significant difference between the groups. Opposite results were seen in a pilot study comparing the mortality between IV vitamin C and the placebo group, which showed a p-value of 0.06 when the Kaplan-Meier survival curve was compared with the Wilcoxon test in patients having a High Sequential Organ failure assessment score (SOFA) (Zhang et al., 2021). Another study conducted on non-COVID-19 patients that were admitted to the ICU with ARDS reported similar results as ours. In this study, vitamin B1 and a high dose of vitamin C were given, but the regime did not improve the mortality benefits (Yoo et al., 2020). As we know, pro-oxidation and inflammatory states are the main cause of ARDS; supplementing vitamin C reduces the risk of activating pro-inflammatory substances and protects against the progression of respiratory membrane damage (Jovic et al., 2020; Talukdar et al., 2020). In our study, we significantly found improvement in levels of CRP, D. Dimer, serum ferritin, procalcitonin, and white blood cell (TLC) levels in Group VC on day four from the start of the treatment. Similar results were reported in other studies conducted on COVID-19 patients treated with a high dose of vitamin C. In a case series, similar work was done in which 1 g of vitamin C was given to 17 patients by IV route every 8hrs for 3 days. The baseline markers were recorded pre-intervention and post-intervention. The comparison showed a significant fall in the inflammation markers. The markers considered were ferritin, D-dimer, and CRP 13. The COVID-19 patients showed severe lymphopenia due to the disturbance in innate immunity response to the excessive production of oxidative stress markers (Yaghoubi et al., 2022). Vitamin C is known to positively affect the immune system as it helps to proliferate T-lymphocytes (Jafari et al., 2019). Due to this potential, it is thought that the supplementation of high doses would inhibit immunomodulation. Our study found stabilization of neutrophils and lymphocyte count between the groups. Our study found that patients in group VC needed less ventilatory support. In a meta-analysis IV, vitamin C shortens the duration of mechanical ventilation, and another RCT demonstrated more days without ventilation in the 28-day study span (Hemilä and Chalker, 2020; Song et al., 2020). Likewise, one study also found that patients receiving vitamin C needed less ventilation 16. Finally, we also compared the length of hospital stay (LOS) between the groups. Although the VC group showed a smaller number of days in hospital when compared with the placebo group. However, statistical results were not significant. The literature showed mixed findings regarding the length of hospital stay (Siordia et al., 2020). It is evident from the literature that vitamin C requirement increases in sepsis and pneumonia because of the enhanced oxidative stress. Vitamin C has been proven to have antioxidant, immune protective, and anti-inflammatory effects when given in a High intravenous dose. Its use in COVID-19 patients to protect respiratory track needs to be tested. More randomized trials are needed to determine the potential of vitamin C in COVID-19. Our study has some limitations as well. We did not assess the vitamin C levels at the start of randomization to determine the initial hypovitaminosis. We also do not measure the levels of antioxidants and reactive oxygen species.

Conclusion

This clinical trial showed that the mega dose of Vitamin C did not improve the P/F ratio and survival. However, it slowed the progression of biochemical markers like D. Dimer, C-reactive protein, and serum ferritin. It also decreases the need for intubation and

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length of hospital stay, but it was not statistically significant in our study.

Conflict of interest

The authors declared an absence of conflict of interest.

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