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Use of Intravenous Vitamin C in Severe COVID led to reduction in ICU stay and severity of Disease

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A B S T R A C T

Background: A global health catastrophe has taken place as a result of the fast spread of COVID-19 throughout the globe. The most prevalent therapy to date has been symptomatic supportive therapy. In clinical studies on patients with bacterial-induced sepsis and acute respiratory distress syndrome (ARDS), a high dosage of intravenous VC (HIVC) was shown to inhibit numerous essential elements of cytokine storm.

Objective: To determine the reduction in ICU stay and severity of disease by using intravenous vitamin C and placebo in patients of COVID.

Methodology: This randomized control trial study was conducted at two different COVID-19 ICU facilities at Ghurki trust teaching Hospital & Mid city COVID center. All the data of patient like name, sex, age and BMI were recorded in a specialized proforma. Patients in Group I received intravenous vitamin C and group II received placebo. Hospital stay was calculated as 14 days or less and >14 days.

Results: A total of 120 patients were enrolled in which 76(63%) patients were males, 38 in each group and 44 (36.6%) patients were females, 22 in each group. In patients of group I, the mean was 58.69±16 years with mean BMI 27.24±4.8 kg/m^2 and mean age in group II was 59.96±20 years with mean BMI 27.98±6.8 kg/m^2. Number of patients in ≤14 days of hospital stay was greater (66.7%, n=40) in Group I, and in group II, 30 (50%) patients were observed.

Conclusion: Our study concludes that the use of intravenous vitamin C in severe COVID affected patients help in reduction of ICU stay and severity of disease as compared to placebo.

Keywords: COVID; Vitamin C; Placebo

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Introduction

Panics about the COVID-19 epidemic have been felt around the world. As of June 21, 2020, 461,715 people have died out of 8,708,008 cases that had been verified globally .1 The most common symptoms reported by infected individuals were fever, cough, dyspnea, and myalgia.[2] According to the findings of a meta-analysis,[3,4] 32.8% of the patients arrived with ARDS (acute respiratory distress syndrome), amongst them 20.3% were moved to the ICU, and in 13.9% patients mortality was observed. An earlier study found that the frequency of non-invasive mechanical ventilation was 41.7% whereas the frequency of invasive mechanical ventilation was 47.22%, and amongst ARDS patients, 66.1% patients with COVID-19 were in the ICU.[3] Nevertheless, since conventional antiviral medications are ineffective against COVID-19, there is presently no particular therapy available. Negative outcomes were seen in recent clinical studies examining novel therapeutics for COVID-19, such as remdesivir, hydroxychloroquine, and lopinavir-ritonavir.[4] Given the dire circumstances, it is imperative that effective medicines be investigated.

Multi-organ failure and death resulting from cytokine storm, endothelial dysfunction and oxidative stress are features of the intricate pathophysiology of COVID-19 infection.[5] Moreover, thiamine deficiency has been linked to lactic acidosis, whereas adrenal insufficiency has been associated with a disordered response of host to infection.[4] Vitamin C is a vitamin that dissolves in water and has many positive effects on the functioning of cells. It acts as an antioxidant, reduces inflammation, and affects the immune system. It enhances the movement and engulfing of neutrophils, reduces the production of pro-inflammatory cytokines caused by lipopolysaccharides, and improves respiratory symptoms during acute infections.[6] Before the pandemic of COVID-19, intravenous (IV) vitamin C was used in experimental settings together with thiamine and hydrocortisone as additional treatment to reduce the metabolic and circulatory disorders.[7-9] Serum vitamin C of 1.5 gm every 6 hours, 50mg of IV hydrocortisone every 6 hours, and 200mg of IV thiamine every 12 hours were administered to critically ill patients in a previous study involving 47 patients. The patients showed statistically significant reductions in death and "Sequential Organ Failure Assessment" (SOFA) score.[7] The significant reduction in death rates and dysfunction of organ was credited to the combined treatment's synergistic impact in reversing the underlying mechanisms of sepsis. This was achieved by suppressing inflammatory mediators, preserving endothelial function, and promoting aerobic metabolism.[10] But the reduction in SOFA scores and death seen in the first study were not replicated in two later multicenter randomized controlled trials investigating the impact of combination treatment on septic shock.[8,10] An observational investigation conducted during the epidemic of COVID-19 in New York found that 66% of the participants experienced shock and needed vasopressor treatment, 39% of patients died, and increased levels of biomarkers of inflammation were a significant predictor of mortality.[11] We hypothesized that the combination of intravenous vitamin C with hydrocortisone and thiamine might have a major impact on the treatment of COVID-19 infection, due to their comparable features and potential for shared disease mechanisms. There is a limited amount of research that has assessed the impact of intravenous vitamin C on the progression of COVID-19 in patients (12,13). In our setting no such study has been carried out therefore this study was carried out to assess the reduction in ICU stay and severity of disease by using intravenous vitamin C and placebo in patients of COVID.

Objective

To determine the reduction in ICU stay and severity of disease by using intravenous vitamin C and placebo in patients of COVID.

Methodology

This randomized control trial study was conducted at two different Covid ICU facilities of Ghurki trust teaching Hospital & Mid city COVID center. The duration of study was six months from 1st January 2021 to 1st June 2021. A total of 120 patients were included in this trial. The inclusion criteria for our study were all the male and female patients of age 20-75 years diagnosed with severe COVID-19 and shifted to ICU while the exclusion criteria were all the patients with dyspnea caused by cardiogenic pulmonary oedema and patients with history of allergy, lactating and pregnant women. After taking informed written consent, detailed demographics including ages, sex and body mass index were recorded. All participants were categorized in two groups as Group I and Group II. In each group 60 patients were included. This study was a randomized trial with two groups. The intervention phase continued for 7 days. In group I, 12g of Vitamin C was mixed with sterile water to make a final volume of 50 mL. It was then infused into the body over a period of 4 hours using an infusion pump. The therapy was performed every 12 hours, resulting in a total daily dose of 24g of Vitamin C for group I. Group II received a placebo, which was 50mL of sterile water. The procedure and rate of administration for the placebo were the same as those for group I. Sterilized water was utilized for both the Vitamin C and placebo to avoid irritating the vein. No additional drugs or treatment plans were employed in this study, except for standard critical supportive care. The intervention started within 12 hours after the participants were enrolled. Hospital stay and mortality among both groups were

Table 1. Baseline demographics details of the enrolled cases

Variable	Group I (n=60)	Group II (n=40)
Gender		
Male	38 (63.3%)	38 (63.3%)
Female	22 (36.7%)	22 (36.7%)
Mean age (years)	58.69±16	59.96±20
Mean BMI (kg/m^2)	27.24±4.8	27.98±6.8

observed as outcomes. The whole set of data was examined using SPSS 24.0. Mean and standard deviation were calculated for age, BMI, IL-6 and CRP level whereas frequencies and percentages were determined for gender, hospital stay and mortality.
The research ethical approval was granted by Ghurki Trust Teaching Hospital institutional review board.

Results

A total of 120 patients were enrolled in which 76(63%) patients were males, 38 in each group and 44 (36.6%) patients were females, 22 in each group. Mean age of the patients in group I was 58.69±16 years with mean BMI 27.24±4.8 kg/m^2 and mean age in group II was 59.96±20 years with mean BMI 27.98±6.8 kg/m^2 (Table1).
Frequency of patients with ≤14 days of hospital stay was greater in Group I. It was 40 (66.7%) in Group I while in group II it was 30 (50%). Based on Hospital stay of >14days, the frequency of patients in group II was greater with 30 (50%) as compared to group I in which 20 (33.3%) patients were observed (Table 2).
We found that CRP level and IL6 in group I was reduced as compared to group II after 1week (Table 3).
Ventilation free recoveries in group I was greater and was found in 35 (58.3%) cases as compared to group II which was observed in 24 (40%) with p value <0.05.(fig 1).
Mortality rate in group I was low and was observed in 4 (6.7%) patients while in group II it was in 6 (10%) patients (Table 4).

Discussion

Previous studies showed that the key mechanism for the patients deterioration with COVID-19 is cytokine storms, which can be blocked by vitamin C[12,13] which is also known for its antimicrobial and immunomodulatory characteristics, historically considered a dietary supplement. In critical care treatment medicine, high dose intravenous vitamin C (HDIVC) has proved to be safe and therapeutic, mainly as an additional treatment for septic shock and multiple organ failure.[14,15] The current study was done with the aim to determine the reduction in ICU stay and severity of disease by using intravenous vitamin C and placebo in patients of COVID.
In the current study a total of 120 patients were enrolled in which 76 (63%) patients were males, 38 in each group and 44 (36.6%) patients were females, 22 in each group. Mean age of the patients in group I (intravenous vitamin C) was 58.69±16 years with mean BMI 27.24±4.8 kg/m^2 and mean age in group II (Control) was 59.96±20 years with mean BMI 27.98±6.8 kg/m^2. Frequency of patients with ≤14 days of hospital stay was greater in Group I. It was 40 (66.7%) in Group I while in group II it was 30 (50%). Based on Hospital stay of >14days, the frequency of patients in group II was greater with 30 (50%) as compared to group I in which 20 (33.3%) patients were observed. These results were comparable to the previous some studies.[16,17] In these studies they reported that the hospital stay was reduced in Vitamin C intervention group as compared to placebo which is in accordance with our study. High dose IV vitamin C is widely used for the treatment of a wide

Table 2. Distribution of hospital stay amongst both groups

Hospital Stay (days)	Group I	Group II
≤14	40 (66.7%)	30 (50%)
>14	20 (33.3%)	30 (50%)

Table 3. Improvement in CRP level and IL6 among both groups

Variables	Group I	Group II
CRP level (mg/L)		
Day 1	13.15±7.16	13.19±8.1
After 1 week	6.88±6.23	10.13±5.64
IL6 (pg/mL)		
Day 1	2.34±5.18	2.55±3.19
After 1 week	1.31±3.14	3.02±6.18

range of diseases, including infections by complementary and alternative medicines. A study of 20,000 patients who received IV vitamin C for two years, found that the average number of infusions per patient was between 19 and 24gm. No definite adverse events have been reported and only few mild adverse effects were reported.[18] Positive results regarding vitamin C treatment for respiratory infections have been reported in clinical trials. Nathens et al. injected 1g of ascorbic acid every 8 hours for 28 days in 594 critically ill patients and observed that the incidence of multiple organ failure and acute lung damage was significantly lower as compared to patients receiving mechanical ventilation.[19] In most critically diseased patients with respiration infection, vitamin C also substantially enhanced the "absolute respiratory score.[20] Fowler et al. reported a case study of 20-year-old women who had respiratory enterovirus/rhinovirus infections that resulted in severe lung damage and ARDS. Twelve hours after extracorporeal membrane oxygenation (ECMO) was started, a high dosage of IV vitamin C was started at 200 mg/kg per 24 hours. This dose was then split into four doses equal to be administered every six hours. By day

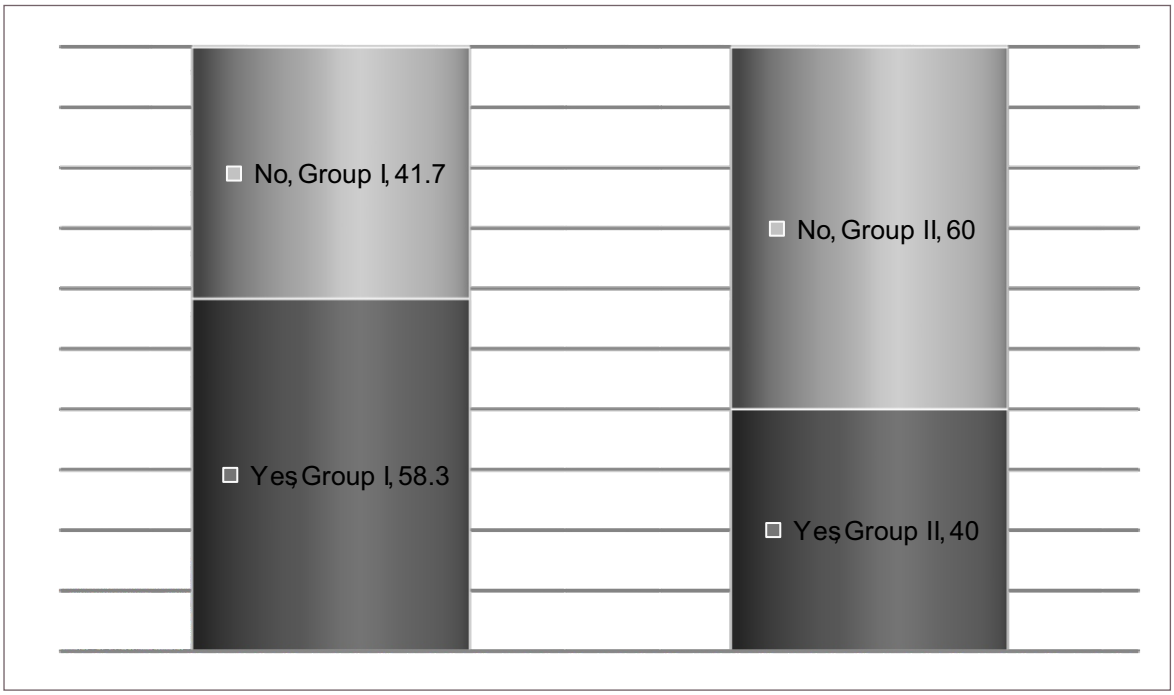

Figure1. Comparison of ventilation free recoveries among both groups

Table 4. Distribution of mortality rate between groups

Mortality	Group I	Group II
Yes	4(6.7%)	6 (10%)
No	56(93.3%)	54 (90%)

seven, the patient had rapidly stabilized, and the mechanical ventilation and ECMO had been discontinued. Following the ARDS, the patient's fibroproliferative sequelae were resolved.[21]

Mortality rate in group I was low and was observed in 4 (6.7%) patients while in group II it was in 6 (10%) patients. These results are in line with the findings of previous study who reported low mortality rate in patients on high dose intravenous vitamin C.[17] The possible mechanisms included the limitation of cytokine surges, the improvement of the clearance of alveolar fluids; vascular injury prevention; restoration of endothelial and alveolar epithelial integrity. Other studies have indicated that infusion of vitamin C can protect patients of acute lung injury (ALI) and ARDS.[21] In our study, ventilation free recoveries in group I was greater and was found in 35 (58.3%) cases as compared to group II which was observed in 24 (40%) with p value <0.05. Previous study with a total of 685 patients showed that vitamin C reduced mechanical ventilation in patients who were seriously ill which is in accordance with the findings of our study.[14] SARS-CoV-2 mainly has a pulmonary and pneumonia impact. The main source of mortality from COVID-19 has been a respiratory failure of ARDS.[22]Simplistic cytokine increase in COVID-19 causes neutrophil sequestration in the lung which damages the alveolar capillary [23,24] similar to septic-induced ALI/ARDS.

Conclusion

Our study concludes that the use of intravenous vitamin C in severe COVID affected patients help in reduction of ICU stay and severity of disease as compared to placebo.

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