Efficacy of intravenous vitamin C in management of moderate and severe COVID-19: A double blind randomized placebo controlled trial

Vijay Kumar¹, Divendu Bhushan¹, Sushmita Supriya¹, Avinash Aravind Ganapule¹, Pallavi Lohani², Shyama¹, Sanjay Pandey², Pramod Kumar Majhi³, Utpal Anand⁴, Ramesh Kumar⁵, Umesh Kumar Bhadani⁶

Departments of ¹General Medicine, ²CFM, ³Pharmacology, ⁴Gastrogurgery, ⁵Gastroenterology and ⁶Anaesthesiology, All India Institute of Medical Sciences (AIIMS), Patna, Bihar, India

Abstract

Aim: To study the efficacy of intravenous vitamin C in management of moderate and severe COVID-19. Objective: To determine the efficacy of intravenous vitamin C in reducing in-hospital mortality in moderate and severe cases of COVID-19. Design: Parallel, double-blind randomized controlled trial with placebo. Ethical clearance was obtained from the institutional ethics committee, AIIMS Patna. The trial was registered with the Clinical Trials Registry - India (registration number- CTRI/2020/11/029230.) Setting: A tertiary care centre in Bihar, India Participants: All patients above the age of 18 years both males and females, admitted in ICU with a diagnosis of moderate and severe COVID-19 (on the basis of a positive reverse transcriptase polymerase chain reaction (RT-PCR) report) at our facility during the study period (01/10/2020–31/12/2020) not having any of the exclusion criteria. Intervention: The patients in the intervention arm were given 1 gram (2 ampoules of 2 ml each containing 500 mg of vitamin C mixed in 100 ml normal saline) intravenous vitamin C 8 hourly for four days. The patients in the placebo arm received similar looking ampoules (2 ampoules of 2 ml sterile water for injection mixed in 100 ml normal saline) intravenously 8 hourly for four days. The rest of the treatment was given as per the standard operating procedure (SOP) of the institute with adjustments as per treating team’s judgement. Outcome Measures: Primary outcome was reduction in in-hospital mortality. Secondary outcomes were improvement in qSOFA score, pO2/fiO2 ratio, fall in inflammatory markers, need for mechanical ventilation and vasopressors. Results: Regarding primary outcome, 10 (33.3%) patients died in intervention group compared to 13 (43.3%) in placebo. Worth noting from baseline characteristics is that 86.7% in intervention group, 11 (36.7%) required invasive mechanical ventilation compared to 14 (46.7%) out of 30 in placebo group but the difference was not statistically significant. Although there were a greater number of moderate cases in placebo group, invasive ventilation requirement (and NIV requirement) was more in this group, thus it could be considered that vitamin C might have a role in reducing the severity of disease. The need for vasopressor therapy was higher in intervention arm compared to placebo, although these results did not reach statistically significant level due to moderate dosage of the drug and small sample size. Conclusion: In the current study, by the observations and results of the double-blind placebo controlled randomised trial, we concluded that as the primary outcome of the study, there was reduction in in-hospital mortality and need for mechanical ventilation in the vitamin C intervention group compared to placebo, although these results did not reach statistically significant level.
statistical significance due to small sample size and use of moderate dose of IV vitamin C. The secondary outcomes of the study such as improvement in organ failure score (qSOFA Score), fall in level of inflammatory markers, improvement in respiratory index (FiO2/ FiO2 ratio), need for mechanical ventilation and need for vaspressors also shown encouraging results but not up to the statistically significant level due to moderate dosage of the drug and small sample size. In summary, high dose of intravenous vitamin C may reduce inflammatory reaction, improve oxygen support status, and reduce mortality in COVID-19 patients, without adverse events. High dose intravenous vitamin C may be a promising therapy for patients of moderate to severe COVID-19.

**Keywords:** COVID-19, intravenous vitamin C, randomized controlled trial

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**Introduction**

The novel coronavirus first reported from Wuhan in China in 2019, causing severe acute respiratory syndrome corona virus-2 (SARS-CoV-2) infection has evolved into an ongoing pandemic affecting almost all regions of the world. The clinical spectrum of COVID-19 can range from asymptomatic cases to critical disease causing acute respiratory distress syndrome (ARDS) and multi organ dysfunction. The disease can progress to pneumonia, respiratory failure, sepsis, septic shock and death when severe. This progression is thought to be related to excessive increase in pro-inflammatory cytokine levels.

A variety of treatment modalities have been tried with varying success in an attempt to retard the progression of the disease. These include corticosteroids such as dexamethasone and methylprednisolone as evidenced by the RECOVERY trial which demonstrated a mortality benefit in moderate to severe cases of COVID-19. Also, the antiviral drug, Remdesivir was demonstrated to shorten the hospital stay. But this was contradicted by the WHO Solidarity trial which did not show any such advantage. Further, the immunomodulatory drug tocilizumab has shown to have a mortality benefit as evidenced by the REMAP-CAP trial.

Multiple other drugs such as ivermectin, azithromycin, montelukast, lopinavir-ritonavir have been used in the treatment of COVID-19 with limited success. Besides, the few drugs that are proven to be efficacious in COVID-19 have an acute scarcity in developing countries such as India, where the pandemic is raging currently.

Due to these reasons, there is a need for utilizing existing drugs which are cost-effective and widely available and repurpose them for use in the current pandemic if they are found to be effective.

Vitamin C is essential for a normal and well-functional host defence mechanism, and pharmacological application of vitamin C is believed to enhance immune function. Previous studies have shown that vitamin C inhibited replication of some viruses such as herpes simplex virus, poliovirus and influenza. There is potential utility in the use of vitamin C in viral infections and possibly COVID-19. After entering the respiratory epithelial cells, the SARS-CoV-2 enhances production of cytokines from virus infected cells and weakens the interferon response. Vitamin C has well-known antiviral effects as it enhances the interferon response of virus infected cells.

Cytokine storm which is the major culprit in severe cases of COVID-19 is characterized by significantly increased levels of inflammatory cytokines especially IL-6, TNF alpha increase oxidative stress in the body leading to lethal lung injury. Vitamin C has a role in reducing the release of pro-inflammatory cytokines, hence alleviating the cytokine storm and associated acute lung injury. It also enhances epithelial barrier function, clearance of alveolar fluid and prevention of sepsis associated coagulation abnormalities.

High turnover of vitamin C in hyperactive immune responses signals the need for supplementation of high dosage of intravenous vitamin C to achieve adequate levels for its effective function.

Several RCTs are ongoing currently with high doses of IV vitamin C (HDIVC). One pilot study has shown potential benefit in oxygenation in critically ill patients of COVID-19.

**Materials and Methods**

The study was aimed at assessing the effectiveness of high doses of intravenous vitamin C in moderate to severe cases of COVID-19. The study conducted was a randomized double-blind placebo controlled trial. Ethical clearance was obtained from the institutional ethics committee, AIIMS Patna. The trial was registered with the Clinical Trials Registry – India (registration number: CTRI/2020/11/029230.)

**Inclusion and exclusion criteria**

All patients above the age of 18 years both males and females, admitted in ICU with a diagnosis of moderate and severe COVID-19 (on the basis of a positive RT–PCR report) at our facility during the study period (01/10/2020–31/12/2020) were included in our study provided they do not meet any of the exclusion criteria which included those with a known allergy or drug reaction to vitamin C or those not willing to participate or those who were a part of other ongoing trials. Pregnant and breastfeeding females were also excluded. Other exclusion criteria were patients previously complicated with end-stage lung disease, end stage malignancy, Glucose-6-Phosphate dehydrogenase deficiency, diabetes mellitus and diabetic ketoacidosis, nephrolithiasis, chronic kidney disease (CKD) and cardiogenic pulmonary edema.

**Definitions of mild, moderate and severe COVID-19 (As per MOHFW Guidelines for COVID-19 treatment)**

Mild: No evidence of breathlessness or hypoxia (normal saturation)
Moderate: Breathlessness and/or hypoxia (saturation 90–94% on room air), respiratory rate of 24 or more and no features of severe disease

Severe: Any of the following – Severe respiratory distress, oxygen saturation <90% on room air, respiratory rate >30, shock or evidence of a life-threatening organ dysfunction.

Methodology

The patients, after obtaining informed written consent, were randomly assigned to either the intervention arm (vitamin C group) or the placebo arm (using block randomisation with variable block sizes of 4,6,8 generated by Sealed Envelope software). The parameters which were noted for all patients at the time of admission included age, sex, pre-existing comorbidities, patient’s symptoms and duration from symptom onset, severity at the time of admission. Other parameters were also noted during the course of hospital stay at variable intervals. Heart rate, blood pressure, temperature, respiratory rate, oxygen saturation were monitored daily. Need for oxygen therapy and method used [face mask, non-rebreathing mask (NRM), high-flow nasal cannula (HFNC), non-invasive ventilation (NIV), invasive mechanical ventilation (IMV)] were monitored every day during the hospital stay; Organ failure scores (qSOFA score) and respiratory index (PaO2/FiO2 Ratio) were recorded before and after intervention. Levels of inflammatory markers like serum lactate dehydrogenase (LDH), procalcitonin, C-reactive protein (CRP), D-Dimer, interleukin-6 (IL-6) and ferritin before and after intervention. Use of any vasopressor agent during hospital course and its duration were also noted.

The patients in the intervention arm were given 1 gram (2 ampoules of 2 ml each containing 500 mg of vitamin C mixed in 100 ml normal saline) intravenously 8 hourly for four days. The patients in the placebo arm received similar looking ampoules (2 ampoules of 2 ml sterile water for injection mixed in 100 ml normal saline) intravenously 8 hourly for four days. Neither the patient nor the treating team or the researchers were aware whether an individual patient has received drug or placebo. Apart from this, standard treatment was given regardless of vitamin C administration depending on the clinical prerogative of the treating physician, to all patients in both the arms, according to their clinical needs and as per the ICMR protocol and SOP of the institute.

Outcome measures

The primary measure of outcome in the trial was in-hospital mortality or discharge. Further, secondary outcomes such as improvement in organ failure score (qSOFA Score), fall in level of inflammatory markers, improvement in respiratory index (pO2/fiO2 ratio), need for mechanical ventilation and need for vasopressors were also assessed.

Sample size and study flow

As shown in study flow chart in [Figure 1], total 126 patients were recruited for study during the study period. Out of these, 58 patients were excluded as they had either diabetes mellitus or chronic kidney disease (CKD). Amongst the rest who were included for the study, block randomization was done with blocks of 4, 6, 8 and patients were divided into either an intervention group or a placebo group. Since this was a pilot study, data regarding similar studies was unavailable at the time the study was planned and all patients presenting to ICU and fulfilling inclusion criteria were recruited during the study period between 01-10-2020 and 31-12-2020.

Statistical analysis

Statistical analysis was done using IBM SPSS (Chicago, USA) software, version 22. All descriptive data were expressed as mean (SD) and frequency (percentage) using student’s t-test. Chi-square test and Fischer’s exact test were performed to assess difference in the primary and secondary outcome measures between the two groups. The clinical parameters were noted on alternate days over a time period of stay of the patients in

Figure 1: Study flow chart
the hospital. The data thus recorded was utilized to calculate two-way repeated measure analysis of variance (ANOVA). A P value <0.05 was considered to be statistically significant. Data analysis was done using SPSS.20 and STATA.12.

Results
Out of those patients admitted in our ICU during the study period, a total of 60 patients were enrolled in the study as they satisfied the inclusion and exclusion criteria. 30 were enrolled in the intervention arm (vitamin C group) and 30 in placebo arm after randomization. There were no dropouts during the study period so all 60 patients were included in final analysis.

Table 1 depicts the baseline characteristics of patients in intervention and placebo arm. There were no significant differences in both groups in terms of baseline characteristics, thus both the groups were comparable. The mean age of the participants was 57 years in treatment arm while it was 63 years in placebo group. Out of 30 patients in treatment group, 26 were male. Similarly, in placebo group, 21 were male. Most of the patients in placebo as well as treatment group, mainly presented with shortness of breath followed by cough and fever. The patients were matched for co-morbidities also. For example, similar number of patients in treatment and placebo group were having hypertension and heart disease. At the time of admission, about five-sixth patient in treatment group were having severe disease while two-third had severe disease in placebo group.

There was also no significant difference in terms of the other treatment given for COVID-19. Almost all the patients were treated with steroid and enoxaparin. Almost similar percentage of patients in both arms were given convalescent plasma therapy and Remdesivir.

Table 2 depicts the comparison of inflammatory markers (CRP, IL-6, procalcitonin, ferritin, D-Dimer, LDH) and respiratory index (pO2/fiO2) pre- and post-intervention in both the arms. As is observed in the table, CRP is reduced in the vitamin C group, whereas there is a rise in the placebo group. Also, there is greater improvement in ferritin and lesser worsening of IL-6 in the vitamin C group as compared to placebo. Only LDH amongst the inflammatory markers showed a worse outcome in the vitamin C group. Further, D-Dimer levels worsened in the vitamin C group, and there was increase in procalcitonin, indicating secondary infection in both groups, more so in the placebo group. Finally, the pO2/fiO2 ratio worsened in both groups, more with placebo. None of these outcomes reached statistical significance though.

Table 3 depicts the comparison of outcome variables, both primary and secondary in intervention and placebo arm. 1/3rd of patients in the vitamin C group had in-hospital mortality as compared to 43% in the placebo group. Lesser number of individuals in vitamin C group progressed to need HFNC, NIV and IMV, thus indicating that the disease progression in vitamin C group might have been partly halted, especially in terms of developing ARDS in COVID-19. However, these outcomes did not achieve statistical significance. Also, vasopressor need was slightly higher in the vitamin C group.

Repeated measure ANOVA was run to assess the improvement in q-SOFA, respiratory rate and mean arterial pressure over 4 time points. These parameters were observed on alternate days. However, the analysis was restricted to only day 3, day 5, day 7 and day 9. The assumption of sphericity was not achieved, thus Greenhouse–Geisser was assessed for P value. It can be deduced from the Table 4 that the aforementioned parameters had improved over time in the treatment group. The mean arterial pressure varied from 94 to 78 mm of Hg and qSOFA decreased to 0.76 from 0.92 in the treatment group. However, the change was not found to be statistically significant.

Discussion
The world is currently facing the threat of the COVID-19 pandemic caused by SARS-CoV-2 infection. This epidemic continues to spread, and there are no vaccines or specific drugs approved or used to prevent or treat COVID-19. A large number of studies have confirmed that high-dose vitamin C can benefit patients with lung injury caused by various inflammatory diseases,

### Table 1: Comparison of Baseline characteristics of Vitamin C and Placebo group

| Characteristics                  | Vitamin C group (n=30) (%) | Placebo group (n=30) (%) | P       |
|----------------------------------|----------------------------|--------------------------|---------|
| Clinico-epidemiological Characteristics |                            |                          |         |
| Mean Age (+SD)                   | 57 (12.8)                  | 63.3 (16.3)              | 0.105   |
| Male                             | 26 (86.7)                  | 21 (70)                  | 0.209   |
| Female                           | 4 (13.3)                   | 9 (30)                   | 0.209   |
| Mean days from symptom onset     | 7.5 (4.5)                  | 6.1 (3.6)                | 0.194   |
| Fever                            | 18 (60)                    | 14 (46.7)                | 0.301   |
| Shortness of Breath              | 25 (83.3)                  | 19 (63.3)                | 0.08    |
| Cough                            | 23 (76.7)                  | 18 (60)                  | 0.165   |
| Generalised weakness             | 4 (13.3)                   | 9 (30)                   | 0.209   |
| Past Medical history             |                            |                          |         |
| Hypertension                     | 13 (43.3)                  | 13 (43.3)                | 1       |
| Heart Disease                    | 2 (6.7)                    | 2 (6.7)                  | 1*      |
| Stroke                           | 0 (0)                      | 5 (16.7)                 | 0.052*  |
| Asthma                           | 0 (0)                      | 3 (10)                   | 0.237*  |
| Hypothyroidism                   | 4 (13.3)                   | 3 (10)                   | 1*      |
| Parkinsonism                     | 1 (3.3)                    | 1 (3.3)                  | 1*      |
| Severity at the time of admission|                            |                          |         |
| Moderate                         | 4 (13.3)                   | 10 (33.3)                | 1*      |
| Severe                           | 26 (86.7)                  | 20 (66.7)                | 1       |
| Treatment Given                  |                            |                          |         |
| Steroid                          | 30 (100)                   | 30 (100)                 | 1       |
| Enoxaparin                       | 30 (100)                   | 29 (96.7)                | 1       |
| Plasma                           | 21 (70)                    | 19 (63.3)                | 1       |
| Remdesivir                       | 27 (90)                    | 27 (90)                  | 1       |
| Tocilizumab                      | 3 (10)                     | 2 (6.7)                  | 1*      |

**Note:** Fisher exact test
Table 2: Comparison of inflammatory markers between Vitamin-C and Placebo group

| Inflammatory markers and respiratory index | Vitamin C group [n=30] | Placebo group [n=30] | P
|-------------------------------------------|------------------------|----------------------|---
| | Pre administration Mean (+SD) | Post administration Mean (+ SD) | | Pre administration Mean (+SD) | Post administration Mean (+ SD) | |
| LDH | 878.45 (305.93) | 903.25 (460.85) | 0.745 | 1124.13 (549.48) | 957.08 (377.74) | 0.114 |
| Procalcitonin | 0.199 (0.189) | 1.275 (4.724) | 0.224 | 0.468 (0.865) | 1.739 (4.519) | 0.149 |
| Ferritin | 834.18 (482.61) | 744.9 (420.44) | 0.208 | 674.88 (548.86) | 661.54 (526.54) | 0.878 |
| D- Dimer | 1.746 (1.44) | 3.941 (6.125) | 0.058 | 3.837 (5.71) | 3.309 (4.46) | 0.539 |
| IL6 | 41.826 (68.41) | 60.288 (92.14) | 0.324 | 42.25 (41.41) | 126.40 (58.11) | 0.07 |
| CRP | 87.695 (82.03) | 61.72 (72.410) | 0.07 | 102.993 (80.43) | 108.889 (120.20) | 0.796 |
| PO2/FiO2 | 147.9 (58.11) | 170.13 (84.39) | 0.039 | 151.267 (68.53) | 178.1 (91.65) | 0.036 |

Table 3: Comparison of Primary and secondary outcome among Vit-C group and Placebo group of COVID-19 patients

| OUTCOMES | VITAMIN C GROUP [n=30] (n%) | PLACEBO GROUP [n=30] (n%) | P |
|----------|-----------------------------|----------------------------|---|
| Primary outcome: | | | |
| In-hospital Mortality | 10 (33.33) | 13 (43.33) | 0.426 |
| Secondary outcome: | | | |
| Vasopressors | 10 (33.33) | 8 (26.67) | 0.573 |
| IMV | 11 (36.67) | 14 (46.67) | 0.432 |
| NIV | 13 (43.33) | 17 (56.67) | 0.302 |
| HFNC | 10 (33.33) | 11 (36.67) | 0.787 |

Table 4: Comparison of clinical parameters at repeated time-points among vitamin-C and placebo group

| Clinical Parameters | Day | Vitamin C | Placebo | F- test (df1, df2) | P |
|---------------------|-----|-----------|---------|-----------------|---|
| q- SOFA | 3 | 0.92 (0.49) | 1.04 (0.47) | 2.41 (1,50) | 0.124 |
| | 5 | 0.68 (0.48) | 0.96 (0.77) | | |
| | 7 | 0.760 (0.52) | 0.96 (0.77) | | |
| | 9 | 0.76 (0.60) | 1.00 (0.80) | | |
| Mean Arterial Pressure (mm of Hg) | 3 | 94.00 (12.65) | 97.67 (8.9) | 0.242 (1,58) | 0.311 |
| | 5 | 93.40 (10.0) | 96.80 (11.1) | | |
| | 7 | 87.96 (19.2) | 93.30 (19.7) | | |
| | 9 | 78.77 (33.4) | 81.15 (33.6) | | |
| Respiratory Rate (per min) | 3 | 26.9 (4.70) | 28.9 (7.61) | 0.933 (1,50) | 0.339 |
| | 5 | 25.35 (4.47) | 28.15 (7.10) | | |
| | 7 | 25.46 (5.08) | 25.61 (6.33) | | |
| | 9 | 24.65 (3.94) | 24.42 (3.88) | | |

especially ARDS and sepsis. This double-blind randomised clinical trial analysed the efficiency and safety of high-dose vitamin C in patients with COVID-19. Vitamin C can directly reduce the production of reactive oxygen species, maintain endothelial barrier function and vasodilation, and downregulate the expression of proinflammatory modulators. Moreover, high-dose vitamin C reduces serum IL-8 level compared with the standard therapy in COVID-19 patients. The synergy of high-dose vitamin C reduces serum IL-8 level compared with placebo, and even lower scores than the patients who received lower-doses of IV vitamin C (50 mg/kg/day administered at 12.5 mg/kg/dose, every 6 hours for four days). In this trial, the patients in the HDIVC group (200 mg/kg/day) achieved plasma levels up to 3,000 µM on day 4.

Patients who received a total of 200 mg/kg/day of HDIVC for 4 days (administered in 50 mg/kg/dose, every 6 hours), had significantly lower organ failure scores than placebo, and even lower scores than the patients who received lower-doses of IV vitamin C (50 mg/kg/day administered at 12.5 mg/kg/dose, every 6 hours for four days). In this trial, the patients in the HDIVC group (200 mg/kg/day) achieved plasma levels up to 3,000 µM on day 4.

However, there were certain limitations in CITRIS-ALI Trial. First, CITRIS-ALI as proposed was based on a previously performed phase 1 safety trial of vitamin C administered to patients in the very early stages of severe sepsis, not ARDS. CITRIS-ALI
enrolment required fully developed ARDS with endotracheal intubation, which could have delayed vitamin C administration in the treatment group and possibly limited the ability to detect an effect on qSOFA scores and biomarkers. Second, CITRIS-ALI may have been underpowered to detect a difference in qSOFA scores and biomarker levels. Third, differences in baseline characteristics of this necessarily heterogeneous population may have influenced mortality. Fourth, the dosage of vitamin C used in this trial (50 mg/kg every 6 hours for 96 hours) may be insufficient for optimal care of sepsis-associated ARDS. Higher vitamin C dosages or longer administration times may have produced different results.

In an ongoing, EVICT – CORONA-ALI Trial (Early Infusion of Vitamin C for Treatment of Novel COVID-19 Acute Lung Injury), they used 100 mg/kg IV vitamin c at every 8 hours for 72 hours.

Raul Hiedra et al. in their study “The Use of IV vitamin C for patients with COVID-19: a single centre observational study” they presented 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. They found the use of IV vitamin C in patients with moderate to severe COVID-19 disease clinically feasible.

Zhang et al. in their study, “Pilot trial of high-dose vitamin C in critically ill COVID-19 patients”, showed that high-dose IV Vitamin C did not improve the primary endpoint Invasive mechanical ventilation free days in 28 days (IMVFD28), but demonstrated a potential signal of benefit for critically ill COVID-19, with an improvement in P/F ratio. They used total 24 grams/day of IV vitamin C for seven days and found it safe and effective.

Liu F, Zhu Y, Zhang J, et al. in their study “Intravenous high-dose vitamin C for the treatment of severe COVID-19: study protocol for a multicentre randomised controlled trial” they used 12 gram of IV Vitamin C at every 12 hourly, total 24 grams of IV Vitamin C for a duration of seven days.

In another study by Jamali Moghadam Siahkali et al. Eur J Med Res (2021) 26:20 “Safety and effectiveness of high-dose vitamin C in patients with COVID-19: a randomized open-label clinical trial” they used 1.5 g vitamin C IV every 6 hours for five days and found that there were improvements in peripheral oxygen saturation and body temperature in both groups during the time of admission.

The current study did not find a statistically significant difference in reducing the in-hospital mortality of moderate to severe patients in intervention group compared to placebo, the most important reason behind this may be the dosage of IV Vitamin C being used in our trial. We used 3 grams/day for four days while several completed and ongoing used 12 to 24 grams/day for four to seven days in different settings. The small sample size may also be another reason to achieve the statistically significant value. However, 10 (33.3%) patients died in intervention group compared to 13 (43.3%) in placebo. Worth noting from baseline characteristics is that 86.7% in intervention arm were of severe category compared to 66.7% severe category patients in placebo group. Though number of severe cases were more in intervention arm there has been comparatively less mortality in this group.

Regarding secondary outcomes, amongst 30 patients in vitamin C group, 11 (36.7%) required invasive mechanical ventilation compared to 14 (46.7%) out of 30 in placebo group but the difference was not statistically significant. Although there were a greater number of moderate cases in placebo group, invasive ventilation requirement (and NIV requirement) was more in this group, thus it could be considered that vitamin C might have a role in reducing the severity of disease. The need for vasopressor therapy was higher in intervention arm 33.3% compared to 26.7% in placebo but not significant statistically.

The secondary outcomes of the study such as improvement in organ failure score (qSOFA Score), fall in level of inflammatory markers, improvement in respiratory index (pO2/fiO2 ratio), need for mechanical ventilation and need for vasopressors also shown encouraging results but not up to the statistically significant level due to moderate dosage of the drug and small sample size.

With respect to changes in inflammatory markers, IL-6 which is a marker of cytokine storm, seems to have increased in both the groups but more significant rise in mean value observed in placebo arm. Ferritin was observed to be in decreasing trend in both intervention and placebo arm with more prominent fall in mean value in the vitamin C group. CRP has shown decreasing trend in vitamin C group while in placebo group, it increased post-intervention. LDH levels reduced in placebo group while increased post-intervention in vitamin C group. Thus, apart from LDH most other inflammatory markers showed better post-intervention outcomes in the vitamin C group as compared to placebo.

All of these secondary outcomes face the same problem with regards to their interpretation as the primary outcome, which is the small sample size. It could be the factor due to which none of these results have been found to be statistically significant.

Procalcitonin, another inflammatory marker more specific for bacterial infections has increased in both the groups, as most patients might have suffered from hospital acquired secondary bacterial infections in this setting, which is a cause for concern. Also, it was slightly worse in the placebo group, which might indicate a role of vitamin C in bacterial sepsis as seen in previous studies.

For respiratory index, pO2/fiO2 is used which has shown increasing trend post-intervention in both vitamin C and placebo groups. Further, trends of other clinical parameters indicated by
qSOFA score, mean arterial pressure, respiratory rate [as shown in Table 4] demonstrate that there was no significant difference with regard to these in between the groups.

**Conclusion**

In the current study, by the observations and results of the double-blind placebo controlled randomised trial, we concluded that as the primary outcome of the study, there was reduction in In-hospital mortality and need for mechanical ventilation in the vitamin C intervention group compared to placebo, although these results did not reach statistical significance due to small sample size and use of moderate dose of IV vitamin C. The secondary outcomes of the study such as improvement in organ failure score (qSOFA Score), fall in level of inflammatory markers, improvement in respiratory index (pO2/fiO2 ratio), need for mechanical ventilation and need for vasopressors also shown encouraging results but not up to the statistically significant level due to moderate dosage of the drug and small sample size.

In summary, high dose of intravenous vitamin C may reduce inflammatory reaction, improve oxygen support status and reduce mortality in COVID-19 patients, without adverse events. High-dose intravenous vitamin C may be a promising therapy for patients of moderate to severe COVID-19.

Multiple studies including ours have indicated favourable outcomes with regards to halting progression of the disease and reducing the need for mechanical ventilation and mortality. Exclusion criteria such as diabetes mellitus especially led to significant reduction in sample size in our study. Cautious use in this setting as well as using different doses of vitamin C in different groups could be implemented in further studies. Future RCT’s with larger sample size could overcome the pitfalls of the current study and lead to a better understanding of the role of IV vitamin C in COVID-19 management.

**Take home message**

Being an inexpensive and widely available drug, the possible application and utility of high-dose IV vitamin C in COVID-19 could be a game-changer.

**Limitations of study**

There were certain limitations in our study, most important of which was the small sample size. First, the study was conducted in the second half of the outbreak of COVID-19 in our country, and the number of qualifying COVID-19 patients decreased with the control of epidemic due to which a larger sample size could not be achieved in our setting during the study period because of the exclusion criteria amongst which diabetes and CKD dominated. Due to small sample size, even though positive results were observed in intervention arm, the numbers yielded no statistical significance.

Secondly, all patients under study received treatments as per AIIMS SOP, the effect of which might have impacted the outcomes which could not be assessed, although the major drugs used were largely similar.

Third, patients received high dose intravenous vitamin C (or placebo) but the time of recruitment for study and initiation of drug varied over the course of hospital stay, meaning some patients were recruited earlier before worsening compared to some who were recruited in a more severe condition. This was mainly due to different timing of transfer to ICU in the course of hospital stay, due to issues such as bed availability. This discrepancy might have affected the outcome amongst this group.

Last but not the least is the total daily dose of vitamin C used in our trial was moderate as compared to all the completed or ongoing trials for the efficacy of IV vitamin C in COVID-19. Most of the study used 12 to 24 grams/day for four to seven days of IV vitamin C as compared to ours where total dose was 3 grams/day for four days.

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**Conflicts of interest**

There are no conflicts of interest.

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