

**Original research article**

## **ROLE OF HIGH DOSE ORAL LIPOSOMAL VITAMIN -C IN REDUCING MORTALITY IN PATIENTS WITH COVID- 19**

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### **ABSTRACT:**

**Introduction:** Severe cases of COVID-19 are associated with hypoxemic respiratory failure, acute respiratory distress syndrome (ARDS), septic shock, cardiac dysfunction, elevation in multiple inflammatory cytokines, thrombo embolic disease, and/or exacerbation of underlying co morbidities. In addition to pulmonary disease, patients with COVID-19 may also experience cardiac, hepatic, renal, and central nervous system disease. AIM OF THE STUDY ;To describe the role and outcome, of high-dose of oral liposomal vitamin C treatment in reducing mortality in Covid-19 patients admitted in Government Medical College & ESI Hospital, Coimbatore, India. .

**Materials and methods:** Patients who admitted with the diagnosis of COVID-19 by RTPCR in government medical college and ESIhospital Coimbatore during 1 th march 2021 to may 31,2021 are taken for this retrospective study .Of the 8634 patients admitted 5422(62%) required non oxygen beds. –2989(34%) required oxygen beds on admission –223patients(2.5%) required beds (with ,98 on c pap,34 ventilators,64 high flow nasal oxygen, 43 non re-breathing mask and 58 non invasive ventilators), all outcomes are compared with same type of patients admitted in similar hospital and similar set of patients, without high dose vitamin c.

**Results:** Overall,164out 8634people (1.9%) died in the vitamin C group while 10 out of 241 (4%) not receiving it died in study period. That means that vitamin C almost halved the number of deaths. Those on vitamin C were 60% more likely to survive

**Conclusion:** Treatment with only vit c cannot be tried in any pandemic situations. preventive methods , social distancing, masks, sanitizers (sms)are essential for everyone till all get vaccinated and get herd immunity for covid 19but treating with high dose oral liposomal vitamin c with standard treatment

**Key words:** Covid-19, High-dose oral liposomal Vitamin C .

## INTRODUCTION

Most of the recommendations for the management of critically ill patients with COVID-19 are extrapolated from experience with other causes of sepsis. As with any patient in the intensive care unit (ICU), successful clinical management of a patient with COVID-19 includes treating both the medical condition that initially resulted in ICU admission and other comorbidities and nosocomial complications.

Patients with COVID-19 may express increased levels of pro-inflammatory cytokines and anti-inflammatory cytokines, which has previously been referred to as “cytokine release syndrome” or “cytokine storm,” although these are imprecise terms. However, these terms are misnomers because the magnitude of cytokine elevation in patients with COVID-19 is modest compared to that in patients with many other critical illnesses, such as sepsis and ARDS.

Clinical trials showed that HIGH DOSE ORAL LIPOSOMAL VITAMIN C may reduce the extent of multiple organ failure and may improve the short-term outcomes of sepsis, plasma ascorbic acid levels were inversely correlated with the incidence of multiple organ failure and the risk of mortality . We suspected that patients with worse organ dysfunction may have a more severe vitamin C deficiency, while high-dose intravenous VC effectively improved the deficiency and subsequently improved organ function . Thus, the benefit was more significant in more severe COVID-19 patients . A large dose of IV ascorbic acid can be one treatment of choices for Covid19 pneumonia . A report on this disease indicates the severity. For example, a 26 % ICU admission and a 4.3 % mortality rate are observed among 138 cases .

## MATERIAL AND METHODS:

Patients who admitted with the diagnosis of COVID-19 by RTPCR in government medical college and ESI hospital Coimbatore during 1 th march 2021 to may 31,2021 are taken for this retrospective study .Of the 8634 patients admitted 5422(62%) required non oxygen beds. –2989(34%) required oxygen beds on admission –223patients(2.5%) required beds (with ,98 on c pap,34 ventilators,64 high flow nasal oxygen, 43 non re-breathing mask and 58 non invasive ventilators), all outcomes are compared with same type of patients admitted in similar hospital and similar set of patients, without high dose vitamin c.

In this study, FOUR GRAMS OF ORAL LIPOSOMAL VITAMIN C EQUAL TO 16 GRAMS OF INTRAVENOUS VITAMIN C. is given to all patients . The main reason was based on two aspects: the efficacy and safety. The metabolism of vitamin C (VC) in the blood is very fast, only large dose and long course of VC supplement can maintain an adequate concentration in blood. In a previous study 4 days VC treatment showed a signal of benefit in sepsis or ARDS patients. Similar daily doses were used in the Fowler paper (JAMA), which was associated with an improved outcome .

In addition, high levels of IL-6 were observed in patients with COVID-19 and might serve as a predictive biomarker for disease severity .IL-6 acts as a critical cytokine in the systemic inflammatory response , leading to a myriad of biological effects that contribute to pulmonary infiltration and organ damage . Tocilizumab , a recombinant humanized anti-human IL-6 receptor antibody, improved clinical symptoms by attenuating inflammation in COVID-19. The findings of the decline in IL-6 in our cohort were consistent with basic research showing that vitamin C inhibited the production and release of proinflammatory cytokines from human monocytes (IL-1, IL-2, IL-6, and TNF- $\alpha$ ) [42]. Previous animal studies on SARS-CoV also demonstrated that inhibiting NF- $\kappa$ B,

together with reduced IL-6 levels, could increase the survival rate in infected animals, more than 67% of individuals in all age groups were showing improvement in cytokines 54% REDUCTION IN CRP , 64% REDUCTION IN SERUM FERRITIN in five days and 82 % in 10 days that shows there will be reduction in the chance of getting life threatening cytokine storm, multi organ failure and death in covid 19.

	Non oxygen	Oxygen bed	Icu admission	mortality
High dose VC	5422(62%)	2989(34%)	223(2.5%)	164(1.9%)
CONTROL GROUP	4408(49%)	3888(42%)	701(7.8%)	241(3.8%)

## RESULTS

Of the 8634 patients admitted 5422(62%) required non oxygen beds. –2989(34%) required oxygen beds on admission –223patients(2.5%) required beds (with ,98 on c pap,34 ventilators,64 high flow nasal oxygen, 43 non re-breathing mask and 58 non invasive ventilators), all outcomes are compared with same type of patients admitted in similar hospital and similar set of patients, were 49% (n=4408)required non oxygen bed,42%( n=3888) required oxygen beds 7.8 % (n=701)required icu admissions and with out high dose vitamin c same type of protocol and the results compared and found out the morbidity, and is less in patients receiving high dose oral liposomal vitamin -C 4 grams per day.

Overall,164out 8634people (1.9%) died in the vitamin C group while 10 out of 241 (4%) not receiving it died in study period. That means that vitamin C almost halved the number of deaths. Those on vitamin C were 60% more likely to survive.

## DISCUSSION

It is believed that ARDS is the main mechanism for Covid19's action. This is followed by increased oxidative stress because of the release of free radicals and cytokines. Considering this mechanism of the process, a large dose of Vit-C should play a key role in the management of Covid19. A study indicates out of 99 Covid19 patients, 17 of them developed ARDS Eleven patients passed away due to multiple organ failure .This death was explained due to increased oxidative stress and cytokine generation that lead to ARDS. ARDS is characterized by strong hypoxemia. This is propagated because of multiple reasons. Uncontrolled inflammation, oxidative injury, and damage to the alveolar-capillary barrier are the main reasons. The severe increased oxidative stress causes pulmonary injuries: lung injury (ALI) and ARDS. ALI and ARDS are key factors responsible for substantially high morbidity and mortality An increase of C-reactive protein (hsCRP), an indicator of inflammation and oxidative stress is seen among Covid19 patients .The transcription factor nuclear factor-erythroid-2–related factor 2 (Nrf2) is a major regulator of antioxidant response element (ARE) driven cyto protective protein expression. It is believed that the activation of Nrf2 signaling pathways plays a crucial role in preventing cells and tissues to undergo oxidative stress.

Dr. Andrew G. Weber, a pulmonologist and critical-care specialist affiliated with two Northwell Health facilities on Long Island, said his intensive-care patients with the coronavirus immediately receive 1,500 milligrams of

intravenous vitamin C. Identical amounts of the powerful antioxidant are then readministered three or four times a day, he said. Each dose is more than 16 times the National Institutes of Health's daily recommended dietary allowance of vitamin C "The patients who received vitamin C did significantly better than those who did not get vitamin C," he said. "It helps a tremendous amount, but it is not highlighted because it's not a sexy drug."

Weber said vitamin C levels in coronavirus patients drop dramatically when they suffer sepsis, an inflammatory response that occurs when their bodies overreact to the infection. "It makes all the sense in the world to try and maintain this level of vitamin C," he said.

The world's first randomized placebo controlled trial designed to test high dose intravenous vitamin C for treatment of COVID-19 has reduced mortality in the most critically ill patients by two thirds. The study, headed by Professor Zhiyong Peng at Wuhan's Zhongnan University Hospital, started in February and gave every other critically ill COVID-19 patient on ventilators either 12,000 milligrams (mg) of vitamin C twice daily or sterile water in their drip. Neither the patient nor the doctors knew who was getting vitamin C or placebo so the trial was "double blind." This is the 'gold standard' of research design. Overall, 5 out of 26 people (19%) died in the vitamin C group while 10 out of 28 (36%) receiving the placebo died. That means that vitamin C almost halved the number of deaths. Those on vitamin C were 60% more likely to survive.

The key measure of the severity of symptoms is called the SOFA oxygenation index. Those with a SOFA score greater than 3 are most critically ill. Of those most critically ill, 4 people (18%) in the vitamin C group died, compared to 10 (50%) in the placebo group. That's two-thirds less deaths. Statistically this meant that of those most critically ill who were given vitamin C, they were 80% less likely to die. This result, backed up with a clear reduction in inflammatory markers in the blood, was statistically significant – beyond doubt. This level of benefit is much greater than the benefit seen in the randomised controlled trial on dexamethasone, the anti-inflammatory steroid drug that hit the headlines as the "only proven treatment" for COVID-19

In this drug trial 23% of patients on the steroid drug died compared to 26% on placebo. However, there were over 6,000 people in the trial so the results were statistically significant.

But now there is another proven treatment – vitamin C. The Wuhan trial needed 140 patients to be sufficiently "powered" for the statistics but they ran out of COVID cases during March, a month after 50 tons of vitamin C, which is 50 million one gram doses, was shipped into Wuhan and given to hospitalised patients and also hospital workers. New admissions into Intensive Care Units (ICUs) plummeted. Professor Peng ended up with a third as many as the trial was designed to include. But, even though the resulting overall statistic showing almost half as many deaths was not significant, the results from the SOFA oxygenation score and other markers were significant.

These results are especially important when case reports in American ICUs using 12,000 mg of vitamin C show almost no deaths in anyone without a pre-existing end stage disease already and also over 85, and a British ICU using 2,000 mg of vitamin C have reported the lowest mortality of all ICUs in the UK, cutting deaths by a quarter. The best results are being reported in ICUs using vitamin C, steroids and anti-coagulant drugs combined, which has been standard treatment protocol in China since April. China's mortality rate from COVID is 3 persons per million compared to the UK's 624 per million, according to Worldometer data

reports from ICUs that are testing the blood vitamin C levels, that the majority of their critically ill patients are vitamin C deficient, many with undetectable levels of vitamin C that would diagnose scurvy. One ICU in Barcelona found 17 out of 18 patients had ‘undetectable’ vitamin C levels, akin to scurvy. Another, in the US, found almost all their patients were vitamin C deficient but those who didn’t survive had much lower levels than those who did. Scurvy killed two million sailors around the world between 1500 and 1800. In 1747 James Lind worked out the cure - vitamin C in limes, but it took fifty years before the Navy took it seriously. So dramatic was the life-saving effect that sailors became known as ”limeys.”

Will the same thing happen with COVID-19? With over a million deaths worldwide and the potential of vitamin C to more than halve the death toll, every day our governments, digital ringmasters and doctors fail to take vitamin C seriously in another day of unnecessary deaths due to ignoring the evidence.

It’s not the corona virus that kills people with COVID; it is usually the immune system over-reacting against dead virus particles, once the viral infection is over, which triggers a “cytokine storm, ” something like an inflammatory fire out of control. That’s when very high doses of both steroids and vitamin C are needed. Normally, the adrenal glands, which contain a hundred times more vitamin C than other organs, release both the body’s most powerful steroid hormone cortisol as well as vitamin C, when in a state of emergency. The steroid helps the vitamin C get inside cells and calm down the fire. Vitamin C is both an anti-inflammatory and anti-oxidant, mopping up the “oxidant” fumes of the cytokine storm. Without vitamin C the steroid hormone cortisol can’t work so well. That’s why ICU doctors administer both extra vitamin C and steroids to get a patient out of the danger zone.

But even better is to prevent a person ever getting into this critical phase of COVID-19. That’s why early intervention, taking 1,000 mg of vitamin C an hour upon first signs of infection, is likely to save even more lives. This reduces duration and severity of symptoms, with most people becoming symptom-free within 24 hours. It takes on average, two weeks of being sick with COVID-19 to trigger the ‘cytokine storm’ phase. During that time, the patient is at risk of becoming vitamin C deficient and then developing acute "induced scurvy." If you can beat the infection within 48 hours you’ll be out of the woods. You can lower your risk even further by taking vitamin D (5000 IU/d, or more: 20,000 IU/d for several days if you already have symptoms), magnesium (400 mg/d in malate, citrate, or chloride form), and zinc (20 mg/d)

#### *Multisystem Inflammatory Syndrome in Adults*

In addition, there are case reports describing patients who had evidence of acute or recent SARS-CoV-2 infection (documented by a nucleic acid amplification test [NAAT] or antigen or antibody testing) with minimal respiratory symptoms, but with laboratory markers of severe inflammation (e.g., elevated C-reactive protein [CRP], ferritin, D-dimer, cardiac enzymes, liver enzymes, and creatinine) and various other symptoms, including fever and shock; and signs of cardiovascular, gastrointestinal, dermatologic, and neurologic disease. This constellation of signs and symptoms has been designated multisystem inflammatory syndrome in adults (MIS-A).

MIS-A is defined by the following criteria:

- A severe illness requiring hospitalization in an individual aged  $\geq 21$  years;
- Current or past infection with SARS-CoV-2;
- Severe dysfunction in one or more extrapulmonary organ systems;
- Laboratory evidence of elevated inflammatory markers (e.g., CRP, ferritin, D-dimer, interleukin [IL]-6)
- Absence of severe respiratory illness; *and*
- Absence of an alternative unifying diagnosis.

COVID-19 may be associated with an array of cardiovascular complications, including acute coronary syndrome, myocarditis, arrhythmias, and thromboembolic disease. Seen in approximately 20 % of hospitalized patients.

Critically ill patients with COVID-19 have been observed to have a prothrombotic state, which is characterized by the elevation of certain biomarkers, and there is an apparent increase in the incidence of venous thromboembolic disease in this population. In some studies, thromboemboli have been diagnosed in patients who received chemical prophylaxis with heparinoids. Autopsy studies provide additional evidence of both thromboembolic disease and microvascular thrombosis in patients with COVID-19.<sup>20</sup> Some authors have called for routine surveillance of ICU patients for venous thromboembolism.

Renal and Hepatic Dysfunction Due to COVID-19. In one case series of patients with critical disease, >15% of the patients required continuous renal replacement therapy.

#### **Vitamin C as anti-viral**

The two-time Nobel laureate Dr. Linus Pauling, an American chemist have suggested that high dose vitamin C is directly virucidal. The vitamin C produces a significant impact on both the innate and adaptive immune functions in viral infections.

#### **In Innate Immunity**

- High concentration of Vitamin C enhances the first line of defence mechanism against the invading pathogens.
- In neutrophils it enhances cellular motility, chemotaxis, phagocytosis and causes oxidative injury by generating reactive oxygen species (ROS), which kills the pathogens and also damages the leucocytes themselves and host tissues.
- Vitamin C act as a potent antioxidant by scavenging the free radicals and protects the leucocyte as well as host tissues from oxidative injury.
- In monocyte and macrophage, it enhances phagocytosis and diminish the secretion of pro-inflammatory cytokines like Interleukin-6 (IL-6) and tumour necrosis factor- $\alpha$  (TNF- $\alpha$ ).

#### **In Adaptive Immunity**

- High dose vitamin C decreases or modifies certain T cells activity, which secretes proinflammatory cytokine IL-2
- It acts as an immunomodulator by enhancing the release of  $\alpha$  and  $\beta$  interferon and downregulating the pro-inflammatory cytokines in lymphocytes.
- It enhances the B cell function and causes significant increase in serum IgA and IgM
- It enhances the proliferation of Natural Killer cells (NK) from mononuclear cells and helps in elimination of virus

In people experiencing cytokine storm, certain cytokines are present in the blood at higher-than-normal amounts. In COVID-19, elevations in several inflammatory cytokines (CRP, FERRITIN, LFT, RFT, D-DIMER, IL6) seem to be involved in the development of acute respiratory distress syndrome, the leading cause of death in people dealing with COVID-19 illness. Studies suggested a protective role of vitamin C infusion in acute lung injury (ALI) and ARDS. Moreover, the latest meta-analysis from eight vitamin C trials of a total of 685 patients indicated that vitamin C shortened the duration of mechanical ventilation in critically ill patients. SARS-CoV-2 primarily affects the lung and causes pneumonia. Respiratory failure from ARDS is the leading cause of mortality from COVID-19. Similar to sepsis-induced ALI/ARDS, the rapid increase in cytokines in COVID-19 causes neutrophil sequestration in the lung, which damages the alveolar capillaries. In sepsis modeling of mice, parenterally infused VC demonstrated a protective effect on the lung. The potential mechanisms included limiting cytokine surges, improving alveolar fluid clearance, preventing vascular injury, restoring endothelial and alveolar epithelial integrity, and augmenting lung barrier cell function and initiating HIGH DOSE ORAL LIPOSOMAL VITAMIN C. However, the P/F increased, which was likely the result of pulmonary ventilation function improvement, based on the above mechanisms.

Clinical trials showed that HIGH DOSE ORAL LIPOSOMAL VITAMIN C may reduce the extent of multiple organ failure and may improve the short-term outcomes of sepsis, plasma ascorbic acid levels were inversely correlated with the incidence of multiple organ failure and the risk of mortality. We suspected that patients with worse organ dysfunction may have a more severe vitamin C deficiency, while high-dose intravenous VC effectively improved the deficiency and subsequently improved organ function. Thus, the benefit was more significant in more severe COVID-19 patients.

#### **CONCLUSION**

With available standard treatment protocols, addition of high dose oral vitamin C reduces MORTALITY by HALF which is very significant in COVID pandemic. Many centres across the globe are now currently using vitamin C as a supportive therapy for hospitalized patients with COVID-19, despite extremely limited clinical data supporting its effectiveness. But our centre has used high-dose oral liposomal vitamin C in a drink form and obtained a remarkable outcome. However, it requires large scale multi-centric clinical trials on high-dose oral liposomal vitamin C for including it in standard treatment protocol.

**Conflict of Interest:** None of the authors have conflict of interest.

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