

Original research article

Study of cytokine storm and high dose liposomal VIT- C in Covid-19

¹Dr.INDHU.K, ²DR.R.RAMARAJ, ³DR.T.RAVIKUMAR, ⁴DR.M.RAVEENDRAN

1. Assistant Professor of Biochemistry, Government Medical College and ESI Hospital, Coimbatore, India
2. Assistant Professor of Medicine, Government Medical College and ESI Hospital, Coimbatore, India
3. Medical superintendent & Professor of Medicine Government Medical College and ESI Hospital, 4. Dean & Professor of Medicine, Government Medical College and ESI Hospital, Coimbatore, India

*Corresponding author

Abstract:

Introduction: Cytokine storm refers to a group of medical conditions in which the immune system is producing too many inflammatory signals, leading to multiple organ failure and death.. The recent outbreak of Covid19 requires urgent treatments for numerous patients. No suitable antivirals are available for Covid19. The efficiency against Covid19 two anti virals developed for other pathologies, is controversial. Therefore, alternative approaches are required. Intravenous (IV) Vitamin C (Vit-C) or high dose liposomal vitamin c orally has emerged as one of the other alternatives for this purpose

Material and methodology: 150 patients with RTPCR Confirmed covid 19 positive without co morbidity with elevated inflammatory cytokines on admission (CRP & FERRITIN) are taken for study. After getting informed consent they were given high dose oral (2 grams) liposomal vitamin C for all, after fifth day and after tenth day the repeat tests were done in the same lab and the results are analyzed.

Results: More than 67% of individuals in all age groups were showing improvement in cytokines 54% REDUCTION IN CRP , 62% 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

Conclusion: As there are no specific treatment available for covid 19 and the cause of morbidity and mortality in covid is due to cytokine storm. with available standard protocols high dose VIT C intravenous or liposomal oral vitamin C is giving promising results , bringing DOWN CRP AND FERRITIN LEVELS provide a potential signal of benefit in oxygenation and even IL-6.. More research are required to optimize the doses and duration of administration.

Keywords: Vitamin C, LIPOSOMAL ,7 Antiviral agents, Covid19, Cytokines

Introduction:

Cytokine storm can cause many different symptoms. Sometimes these are only mild, flu-like symptoms. Other times, these can be severe and life-threatening. Symptoms might include:4 Fevers and chills, Fatigue, Swelling of extremities, Nausea and vomiting, Muscle and joint aches, Headache, Rash, Cough, Shortness of breath Rapid breathing Seizures, Tremor, Difficulty in coordinating movements, Confusion and hallucinations ,Lethargy and poor responsiveness, Very low blood pressure and increased blood clotting can also be hallmarks of severe cytokine storm syndrome. The heart may not pump as well as it normally would. As a result, cytokine storm can affect multiple organ systems, potentially leading to organ failure and death.

In cytokine storm syndrome, respiratory symptoms may worsen to become acute respiratory distress syndrome (ARDS), which might require mechanical ventilation. Cytokine storm is not considered a disease in itself, but rather a serious medical issue that can happen because of several different underlying issues. Cytokine storm has received more attention because of the COVID-19 pandemic. Cytokine storm seems to be at least part of the reason some people develop life-threatening symptoms from COVID-19.

Cytokine storm is a cascade of exaggerated immune responses that can cause serious problems. The immune system contains many different components that help you battle infections. It includes many different types of cells that communicate with each other via signaling molecules, known as cytokines. There are many different cytokines that perform many kinds of functions. Some help recruit other immune cells, and some help with antibody production or pain signaling. Some make the blood clot more easily. Some help produce inflammation, which can make blood vessels more leaky than normal. Another group of cytokines helps tamp down the body's inflammatory response. That's an important balance, since too much inflammation causes its own problems. Under normal circumstances, these cytokines help coordinate the response of your immune system to take care of infectious substances, like viruses or bacteria. The problem is that sometimes the body's inflammatory response can get out of control, causing more harm than good.

Sometimes the body produces too many inflammatory cytokines and not enough cytokines that modulate inflammation. The inflammatory cytokines start "storming" out of control, without enough feedback from the anti-inflammatory cytokines.

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

Methodology:

In this study, TWO GRAMS OF ORAL LIPOSOMAL VITAMIN C EQUAL TO 8 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- α) [42]. Previous animal studies on SARS-CoV also demonstrated that inhibiting NF- κ B, together with reduced IL-6 levels, could increase the survival rate in infected animals .

SARS-CoV-2 infection was characterized by mild symptoms initially, followed one week later by a rapid deterioration leading to hospitalization, and ARDS always occurred at the day 8 after the first symptom . vitamin C has direct antiviral activity against SARS-CoV-2.

Results:

TABLE 1: Age distribution(n=150)

Age Group	Number of Patients	Percentage
≤ 30 Years	36	24%
31-40 Years	51	34%
41-50 Years	27	18%
51-60 Years	24	16%
61-70 Years	12	8%

TABLE 2: Sex distribution

Sex	No of Patients	Percentage
Male	61	61%
Female	39	39%

TABLE 3: Signs and symptoms

Signs and symptoms	No of patients	Percentage
Fever	63	42%
Chills	9	6%
Sore throat	27	18%
Dry cough	27	18%
Shortness of breath	12	8%
Abdominal pain	6	4%
Diarrhoea	12	8%
Anosmia	6	4%
Myalgia	54	36%
Tiredness	60	40%
Asymptomatic	48	32%

TABLE 4: Days on which both cytokine reduced

No of days	No of patients	Percentage
≤5 days	81	54%
>10 days	54	36%

TABLE 4: Days on which CRP reduced

No of days	No of patients	Percentage
≤5 days	94	94%
>10 days	24	16%

TABLE 4: Days on which FERRITIN became normal

No of days	No of patients	Percentage
≤5 days	96	64%
>10 days	24	16%

TABLE 4: Days on which RT-PCR became negative

No of days	No of patients	Percentage
≤8 days	92	92%
>14days	8	8%

150 patients with RTPCR Confirmed covid 19 positive without co morbidity with elevated inflammatory cytokines on admission(CRP &FERRITIN) are taken for study.After getting informed consent they were given high dose oral(2 grams) liposomal vitamin C for five days and ten days the repeat tests are done in the same lab and the results are analyzed. 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.

Discussion:

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 . 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. Like influenza, coronaviruses are pandemic viruses that injure lung drastically . This viral infection generates a “storm” of cytokines that reacts with the endothelial cells of the lung. This interaction causes neutrophil infiltration and enhances oxidative stress and damages the function of the lung barrier. 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.

Laboratory abnormalities, like may be seen in basic blood tests, can provide clues. People with cytokine storm might have abnormalities like the following:

- Decreased number of wbc
- Elevations in markers of kidney or liver damage(LFT RFT)
- Elevations in inflammatory markers like C-reactive protein (CRP)
- Abnormalities in markers of blood clotting(D-DIMER)
- Elevated ferritin (involved in infection response)

Medical imaging can also provide clues. For example, a chest C.T scan might display lung involvement from cytokine storm related to COVID-19.

Chest X-ray and CT Scan for COVID-19 (Coronavirus)

Supportive care is a critical part of treatment for cytokine storm. If an individual is experiencing severe symptoms (like difficulty breathing), they may need care in an intensive care unit. This might include support such as the following:¹³

- Intensive monitoring of vital signs
- Ventilatory support
- Fluids given intravenously
- Management of electrolytes
- Hemodialysis
- Aspirin
- Corticosteroids
- Drugs that affect the immune system, like cyclosporine
- Biological therapies that block specific cytokines
- Plasma exchange (plasmapheresis)
- Statin drugs and finally

HIGH DOSE LIPOSOMAL VITAMIN C ORALLY OR INTRAVENOUS VIT C

Researchers are actively exploring many different therapies to treat cytokine storm syndrome from COVID-19. Many are studying existing therapies that affect the immune system to see if any might help people with cytokine storm from COVID-19.

For example, Kineret (anakinra) is a biologic therapy sometimes used to treat people with rheumatoid arthritis and other medical conditions that can affect the immune system. It blocks the activity of a specific cytokine known as interleukin 1 (IL-1). It has sometimes been helpful for people with cytokine storm from autoimmune conditions.

Researchers are currently studying whether this therapy might help critically ill people with cytokine storm syndrome from COVID-19.

Another example is Actemra (tocilizumab), a biologic that can be used for rheumatoid arthritis and other conditions. This therapy blocks the activity of another cytokine, interleukin 6 (IL-6). Actemra has previously sometimes been used to treat cytokine storm resulting as a side effect of therapy (like for leukemia).⁴

Scientists are currently investigating these therapies, as well as many other potential interventions. Ideally, multiple therapies will be found to help curb the effects of cytokine storm, leading to decreased deaths from COVID-19.

Conclusion

In summary, this study showed that HIGH DOSE ORAL LIPOSOMAL VITAMIN C demonstrated a potential signal of benefit for critically ill COVID-19, with an improvement in P/F ratio. Nevertheless, further large-scale RCTs are still needed to confirm our understanding of the effect of HIGH DOSE ORAL LIPOSOMAL VITAMIN C therapy in critically ill patients with COVID-19. The protocol using intravenous high dosage of vitamin C, thiamine and a glucocorticoid (as dexamethasone) seems to be useful, not expensive, with low risk of severe adverse effects. The aim is providing further discussion about the recovery of complicated cases of cytokine storm associated to the SARS-CoV-2.. It is believed that IV Vit-C has been particularly effective by inhibiting the production of cytokines storm due to Covid19.

Conclusion:

Covid-19 pneumonia is an extremely rapidly developing disease with a high mortality rate. The main pathogenesis is the acute lung injury that causes ARDS and death. Antioxidants should have a role in the management of these conditions. Appropriate clinical studies and reports demonstrate that a timely administration of high dose IV Vit-C improves the outcome of Covid19 infection.

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