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A LITERATURE REVIEW: USE OF VITAMIN C IN THE PREVENTION AND THERAPY OF CORONA VIRUS (COVID-19) INFECTION

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ABSTRACT

Corona virus disease 2019 has spread very rapidly in the whole world. It has affected almost all countries with high rates of mortality. It has been found that the causal agent of this disease is SARS Co- V. It is found to affect the respiratory system badly with failure of various organs. The inflammatory reaction is the main cause of acute respiratory distress syndrome and multiple organ failures in patients with corona virus disease, 2019, especially those with severe and critical illness. Several studies suggested that the high dose of Vitamin C reduced inflammatory reaction associated with sepsis, pneumonia COVID-19 .It has been seen that Vitamin C reduce the oxidative distress, protects epithelial lining of the respiratory tract and many other pharmacological properties. Due to such properties it can be used in treatment of COVID-19 infection. Vitamin C has been seen to have very promising outcome when given in early stages of the infection.

KEY-WORDS: - Vitamin C, Oxidative stress, Cytokines storm, Remdesivir.

INTRODUCTION

The corona virus disease 2019 (COVID19) pandemic was started in late 2019 and spread out throughout the world dangerously with many people sacrificed their lives. Many countries lost a lot of people with flooded hospitals with patients and other health issues. Experiencing such scenario food supplements has been suggested by the health system to boost immunity so that the human body could fight with it.

Vitamin C is a water soluble essential vitamin which is not synthesized in the human body. It is also known as ascorbic acid. It is present in some food items like citrus fruits and also available as a supplement in the market. With the start of Covid 19 pandemic no effective drug is available for SARS CoV infection. Food and Drug Administration (FDA) has approved use of Remdesivir injections for the treatment of Covid 19 patients. In such

situations the use of supportive therapy is very useful. The use of micronutrients like vitamin c has therefore got attention for such kind of therapy. It is antioxidant, antiviral, anti-inflammatory and has immunomodulatory effects. There are several countries like USA and China, undertaking the pharmacological characteristics, used vitamin C as the main supplement to fight against the Covid 19 viral infection. SARS-CoV-2 infection stimulates the immune system and is responsible for oxidative stress which results in release of cytokines leading to cytokine storms. This leads to lung damage which subsequently leads to adult respiratory distress syndrome. As vitamin C is an antioxidant and has immunomodulatory effect, it can be used against SARS CoV-2 infections.

OBJECTIVES

- To know the pharmacological properties of Vitamin C.
- To find out the potential of Vitamin C to overcome COVID-19
- To find out the antiviral properties of vitamin C which might be used in diseases like sepsis, pneumonia and COVID -19?

RESEARCH METHODOLOGY

To achieve the objectives, the researcher has reviewed many research papers, research articles, medical reports, medical letters, government and non- government data and reports of clinical trials.

VITAMIN C AS ANTIOXIDANT- Many evidence makes clear that Vitamin C has antioxidant properties. It is a scavenger of oxygen free radicals. Vitamin C helps to maintain redox integrity of the cells thus protecting the lungs from oxidative stress caused by infection of SARS Co V- 2 virus. Proinflammatory and pro- oxidant are the main pathological processes that lead development of ARDS. High dose of vitamin C can have a pro-oxidant effect; as shown by many clinical trials, it can be effective to prevent the situation of ARDS. This leads to strong fight with Covid 19 virus and thus vitamin C is considered to be very effective in preventing SARS CoV infections.It also intensifies the antioxidant effect of polyphenols in the body.Vitamin C supplement of 600mg daily reduced the incidences, severity and duration of URTI after ultramarathon race.

ANTIVIRAL PROPERTIES OF VITAMIN C - Ascorbic acid has a huge role in antiviral and immune enhancement activities. It has been proven that Vitamin C is important for production of type I interferon during the antiviral immune response. According to recent studies of B.X. Hoang et.al.(2020) , vitamin C is useful in upregulating the natural killer cell and cytotoxic T- lymphocyte activity both in vitro and in vivo. It has potential to inactivate the fixed rabies virus. Other studies have used this vitamin as an inactivating agent both for RNA and DNA viruses. A study done by A. Abobaker has shown that high dose of Vitamin C have a veridical activity because it inactivates the viral multiplication in vitro.The virucidal effect of vitamin C is not confirmed in vivo. It has been that various viral infections can be controlled by the use of Vitamin C. It includes the decreased activity of Esptein-barr Virus(EBV) early antigen, and supressed EBV viral load.Vitamin C with no combination of other

antivirals, suppressed viral replication of herpes simplex virus-1.In another in vitro study, it has been seen that a nutrient mixture including vitamin C has a dose dependent suppression effect on production of influenza viral nucleoproteins and neuraminidase activity. In vitro exposure of the chick embryo tracheal organ to vitamin C had increased resistance of infection to corona virus.

It is argued that regular use of vitamin C supplement reduced the duration of common cold symptoms. Conceptually, it is believed that vitamin C has potential to prevent upper respiratory tract infection (URTI).It is because of its capacity to reside in epithelial lining where it performs the work of local mucosal protecting agent. Sepsis is very deadly disease which causes multiple organ failure. This disease is very difficult to handle for critically ill patient as it requires mixture of treatments along with supportive care. Fisher et al. has shown by the studies on mouse that vitamin C restricts the failure of multiple organs together. With to mice experiment, he demonstrated the mice with vitamin C supplement have not shown any sign of organ failure but other without supplement die due to organs failure. The protection against sepsis is due to the fact the vitamin C helps in synthesis of vasopressor norepinephrine and vasopressin.In condition of sepsis shock, the patient does not require external vasopressin as these endogenous vasopressors help in vasodilation during sepsis regulating blood pressure. It is hypothesised that oral vitamin C supplement combined with its inhalation which maintains high levels of vitamin C in bronchial epithelium and respiratory secretions could have protective action against influenza virus infection.

VITAMIN C AS IMMUNOMODULATOR - Vitamin C has a lot of potential of improving the immunity system as well as humoral response.Vitamin C enhances epithelial barrier integrity which is first line of defence against the external pathogen.Vitamin C is helpful in enhancing the activity of natural killer cell activity which is very important activity against the viral infections.Vitamin C when taken in high dose is helpful in maintaining the leukocytes as it gets accumulated intracellularly in neutrophils.Improved chemotaxis has been seen to improved by giving 1g/day of IV Vitamin C for 6 months to the asthamatic children(A.Abobaker,2020). It has also been shown by the experiment the neutrophilic phagocytic activity has been improved by using vitamin C supplement in a dose of 200 mg to 1 g daily for 1-4 months.but administration of vitamin C in a dose of 2 g on a daily basis for 2 week the bacterial killing activity of neutrophil gets impaired.Thus, Vitamin C could enhance the phagocytic activity, epithelial barrier integrity, natural killer cell activity and Chemotaxis of neutrophils, it's administration could enhance the innate immune response against SARS- Co-V 2 infection.

Many Studies have shown that a person deficient in Vitamin C has imparied cellular and humoral immune response(Mousavi S.et.al,2019). It has also been shown that if vitamin C supplements are taken in amount of 1000 mg daily for 42 days then there is significant reduction in free radical induced DNA damage in peripheral blood lymphocytes (Brennan L, Morris G, Wasson G, Hannigan B, Barnett Y, 2000).Vitamin C deficiency related with the age is associated with low IgG and IgM serum levels(Jayachandran M, Rani P, Arivazhagan P, Panneerselvam C.2000)But if Vitamin C supplement of 200 mg/day is taken for 1-3 months then the levels of IgG and IgM serum levels are increased and that resulted in improvement of humoral immune response in elderly person.A study on animals has shown that vitamin C has inhibited the negative immunoregulatory effect of T regulatory cells which in turn T regulatory cells which resulted in enhanced T cell mediated response leading to improved sepsis and sepsis induced multi organ failure (Gao Y, Lu B, Zhai J, Liu Y, Qi H, Yao Y, et al,2017). It has seen that the

immunological effect of SARS Co V -2 is negative which decreases the numbers of natural killer cells in addition to inducing excessive release of inflammatory mediators leading to cytokine storm and tissue damage. In this regard, vitamin C is considered to be the best supportive therapy. It decreases the severity of SARS Co- V 2 infection and decreases the duration of illness.(Wang L, Wang Y, Ye D, Liu Q,2019)

VITAMIN C AS A SUPPORTIVE THERAPY FOR MANAGEMENT OF COVID-19 - Use of IV Vitamin C shows good results in COVID 19 patients. Using a high dose of Vitamin C decreases the risk of cytokine storm during late COVID-19 infection.(Boretti A, Banik B.,2020). Vitamin C in combination with curcumin and glycyrrhizic acid enhanced innate antiviral immunological response and prevented excessive inflammatory-induced tissue which decreased the risk of inflammation-induced tissue damage.(Chen L, Hu C, Hood M, Zhang X, Zhang L, Kan J, et al,2020). In Burn injury patients, administration of Vitamin C has helped to restore endothelial function and resuscitative IV fluid requirements(Rizzo J, Rowan M et al,2016). Severe SARS - Co-V -2 infection leads to endothelial damage and dysfunction which consequently increases the risks of development of widespread micro and macrovascular thrombosis and multiple organ failure(Pons S, Fodil S, Azoulay E, Zafrani L,2020). Vitamin C is thus might be used to reduce the risks of COVID 19 viral infection as it has ability to restore endothelial function. Treatment of IV Vitamin C as a monotherapy, might help to reduce lungs inflammation and lung injury in COVID- 19 (Hernández A, Papadakos P, et al,2020).. A significant improvement was noticed compared with patients who did not receive IV Vitamin C treatment . Cheng et al, recommended early administration of high dose of Vitamin C treatment of COVID 19 pneumonia.

EVIDENCES FROM DIFFERENT CLINICAL TRIALS - The pilot trails of high dose of vitamin C on critically ill COVID -19 patients studies by Jing Zhang,Xin Rao , Yiming Li, et al. have shown that the addition of 24 g per day for 7 days intravenously vitamin C may provide a potential signal in oxygenation and IL-6.The meta analysis on eight vitamin C trails of a total of 685 patients have shown that Vitamin C shortens the duration of mechanical ventilation in Critically ill patients (Hemila H, Chalker E,2020).The result of pilot trails have shown promising results that the implementation of high dose of Vitamin C improved oxygenationation in critically ill patient with COVID-19 by improving PaO2/FiO2.

It is worthy to note that some studies have used higher doses of vitamin C in their patients (Zhang J, Rao X, Li Y, Zhu Y, Liu F, Guo G, et al,2020). The highest dose was used in the work of Zhang et al. who have used 24 g daily in the form of 12 g of vitamin C/50 ml every 12 h for 7 days at a rate of 12 ml/h. Although they did not find superior results in terms of improving invasive mechanical ventilation-free days in 28 days (IMVFD28), but have found improving PaO2/FiO2 and hence benefiting oxygenation for critically ill patients [39]. Marik et al. also suggested the MATH+protocol for COVID-19 patients, including methylprednisolone, ascorbic acid, thiamine, heparin, and supplemental oxygen. They suggest using vitamin C 3 g IV q 6 hourly for at least 7 days or until transferred out of ICU . There are also other large randomized controlled trials (RCTs) using different doses of vitamin C.(Jamali,Moghadam, Siahkali et,2021). In another clinical trial by Dengfeng Gao, Min Xu, Gang Wang et al (2020), it has been shown that the risk of 28 day mortality was reduced for the high dose of Vitamin C versus the standard therapy group was reduced. Oxygen support status was improved more with the high dose of Vitamin C than standard therapy. No safety events were associated with the high dose of Vitamin C therapy.

SAFETY PROFILE OF VITAMIN C - The recommended dose of Vitamin C in adults is 90 mg/day(Bakare TA, Soar JS,2020). At the time of acute infection, higher dose of Vitamin C is required to overcome the infection. According to the United States nutritional recommendations, the tolerable upper limit of the daily dose of Vitamin C is 2g (Hemilä H, Louhiala P,2007). If a person takes high dose than the recommended one then it results in diarrhoea, abdominal pain and nausea.(Kim S, Yeom J.,2020). A dose of 10g/day results in higher risk of oxalate nephropathy and kidney stone. (Nabzdyk C, Bittner E,2018).It is very interesting to note that the clinical trials on sepsis patients has shown no adverse effect including kidney stones.(Kashiouris M et al,2020). This can be explained by the fact that Vitamin C is water soluble, therefore, intoxication due to excessive Vitamin C which exceeds the body daily requirement will be excreted by the kidneys.

The excessive use of Vitamin C than the recommended level may interfere with the reading of glucometer and its accuracy may get affected . The molecular structure of glucose and Vitamin C has many similarities. Due to this the condition of hypoglycemia may get missed.(. Hager D, Hinson J, Rothman R,2020). Thus laboratory blood samples or venous blood gases are taken into consideration for measurement of blood glucose in patients to avoid the missing of the condition of hypoglycemia (Kuhn S, Meissner K, Mayes L, Bartels K , 2018). Therefore a high dose of Vitamin C must be taken with the caution as it resulted in renal impairment and might increase the risk of toxicity. But the side effects of high dose of Vitamin is almost negligible. (Abat M, Larracas C, Cabaluna I,2020).Therefore, the benefit of using high dose of Vitamin C as part of the supportive management of COVID- 19 hugely overweighs the risk of development of adverse reactions. (A. Abobaker et al.,2020)

CONCLUSION

From all the studies, it can be concluded that the administration in IV Vitamin C in COVID 19 patients decreases the duration of illness. Vitamin C might have an antiviral effect against multiple respiratory viruses in addition to other DNA and RNA viruses such as Herpes, HIV and Sepsis viral infection. It has been also seen that if Vitamin C is taken in a recommended dose then it is present in the epithelial lining of the respiratory tract where it acts as a protective layer of nasal cavity thus decreasing the risk of infection. It has virucidal activity which also support the fact that use of vitamin C is helpful in therapy of SARS Co-V-2. Low Vitamin C level also have been correlated with higher mortality in other individuals from causes like cardiovascular disease. High oxidative stress, a major factor in conditions like cardiovascular diseases as well as aging and now COVID -19 ,also associated with significantly reduced expression of the Vitamin C transporter. But high doses risks cannot be ignored thus the administration of Vitamin C in Patients of COVID - 19 can be accepted as a supportive therapy. Further studies are suggested for administration of Vitamin C to critically ill patients under recommended dose.

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