

Original research article

High dose vitamin- C in Covid-19 induced neuro- cognitive dysfunction

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ABSTRACT:

BACKGROUND: The current pandemic Covid-19 causes several clinical manifestations from asymptomatic presentation to more serious Severe Acute Respiratory Syndrome (SARS) . There is no specific antiviral treatment for Covid-19 and the management is mainly symptomatic. The symptoms mainly include many neurological as well as cognitive impairment in majority of patients.

AIM :The study aims to find out the covid induced neurological symptoms and cognitive dysfunction and the role of high-dose of oral liposomal vitamin C in patients admitted in Government Medical College & ESI Hospital, Coimbatore, India.

MATERIAL: All the patients admitted with positive covid19 confirmed by RTPCR are randomly selected and included in study age between 18years to-60years only are included , male and female total number 150 are taken for study after getting informed consent.

RESULTS: More than one Neurological Symptoms are experienced by 12-88% of patients and Cognitive Impairment by 82% of people. By Administrating Symptomatic treatments and supplements with 2 gms of liposomal Vitamin –C in a palatable juice form , 76 % of them improved within 5 days rest of them in 10 days.

.CONCLUSION: Vit-c is most under estimated vitamin. It is cheap, easily available, more efficient and helps the body to fight against covid -19 too. High dose intravenous as well as oral liposomal vitamin-C is more effective in protection and recovery from covid -19 induced neuro-cognitive dysfunction.

KEY WORDS: Covid-19, High-dose oral liposomal Vitamin C, NEURO cognitive dysfunction

INTRODUCTION

Cognitions are thinking skills or intellectual abilities used for perceptions, acquiring, understanding, and responding to information presented to a person. Cognitive dysfunction, or brain fog, is the loss of these intellectual abilities. This can affect a person's thoughts, memories, language; verbal fluency; and psychomotor speed and reasoning capabilities. This disorder can manifest as trouble with recalling words, with the ability to do math problems, and with one's focus. However, the cause has been linked to pathogens, such as bacteria or viruses that affect the immune system. Some forms of cognitive dysfunction are temporary and improve over time as the disease or disorder begins to improve but some worsen without improvement at all.

Vitamin C (ascorbic acid) is a water-soluble vitamin that is thought to have beneficial effects in patients with severe and critical illnesses. It is an antioxidant and free radical scavenger that has anti-inflammatory properties, influences cellular immunity and vascular integrity, and serves as a cofactor in the generation of endogenous catecholamines. The biological mechanisms of vitamin C on brain and neuronal functioning have been well established. It is a vital co-factor in numerous processes such as the biosynthesis of collagen, carnitine, tyrosine, peptide hormones as well as myelin. Vitamin C plays a crucial role in neurotransmission and neuronal maturation and functions.

During human evolution, vitamin C lost its synthesizing capacities in humans due to the mutation in L-gulono- γ -lactone oxidase (GLO) gene, which codes for the vitamin C biosynthesis. So, the benefit of vitamin C to the human body is achieved by external sources, which is abundant in Indian gooseberry, limes, oranges, lemon, tomatoes, kiwifruit, potatoes and leafy greens. Since it is a water-soluble vitamin, the oral bioavailability of regular vitamin C is only 15-30%. But the advent of nanotechnology liposomalized vitamin C has more than 90% absorption. The liposomes are novel delivery system composed of phospholipid of soy or sunflower lecithin, which carries vitamin C into the intestinal cells with higher absorption rate and increases vitamin C in the blood level.⁶ The excess amount of vitamin C excretes freely in urine. The recommended daily allowance in male is 90mg and in female is 75mg. The tolerable upper limit of oral vitamin C is 2gm per day without gastrointestinal disturbances. But there is no scientific evidence of toxicity even in the dosage of 10gm per day⁷.

MATERIALS AND METHODS

Study Population

Patients who admitted due to COVID-19 with neurological complaints with cognitive impairment around 150 participants were included. Cross sectional Observational Study was conducted to evaluate all patients have received high-dose of oral vitamin C with lecithin composition in a drink form. Each juice box contains 200ml with 1gm of liposomal vitamin C. The patients were treated by giving 2 juice boxes in the morning as well as in the evening. Totally 4gms of liposomal vitamin C has given daily for 10 days.

Methods:

The medical records of patients were analysed by the research team of the Department of Medicine, Government Medical College & ESI Hospital, Coimbatore, India. The epidemiological, clinical, laboratory, treatment and outcome data were obtained with data collection from electronic medical records. All data was reviewed by internal medicine specialists. All patients were tested for Covid-19 from a nasal swab by real time reverse transcription polymerase chain reaction (RT-PCR) assay of 2019-nCoV RNA. Primary outcomes of cognitive functions were studied by below given scorings and calculations.

Criteria

Inclusion Criteria:

- Hospitalized with diagnosis of COVID-19, diagnosis confirmed by PCR test
- Older than 18 year, less than 60 years.

Exclusion Criteria:

- Renal failure
- Hepatic failure

- End-stage malignancy
- Presence of diabetic ketoacidosis, use of insulin infusion, or frequent need for point-of-care glucose monitoring (>6 times/24 hour period) as determined by treating physician.
- Spo₂ < 94 % and Critically ill admitted in ICU

Primary Outcome Measures :

- short term memory testing
- mini mental score
- simple arrhythmic calculations
- problem solving

PATHOPHYSIOLOGY:

Neuro inflammation is believed to be one of the primary causes of cognitive impairment. Previous studies showed that the antioxidant vitamin C (Vit C) performs many beneficial functions such as immune stimulant and anti-inflammatory actions, but its role in inflammatory cognitive impairment is unclear. In one of the study conducted, it was investigated the effect and possible mechanism of action of Vit C in lipopolysaccharide (LPS)-induced cognitive impairment. Intracerebro-ventricular LPS-induced memory impairment was used as the model for neuro-inflammatory cognitive dysfunction. Vit C was administered by intracerebro-ventricular microinjection 30 min prior to LPS exposure. It was found that Vit C significantly protected animals from LPS-induced memory impairment. Vit C pretreatment inhibited the activation of microglia and the production of pro-inflammatory cytokines, including tumor necrosis factor- α (TNF- α) and interleukin-1 β (IL-1 β). Furthermore, Vit C pre treatment markedly decreased the malondialdehyde (MDA) level, increased superoxide dismutase (SOD) activity, and modulated the Bax/Bcl-2 ratio and p-p38 MAPK activation in the hippocampus of LPS-treated mice. Together, these results suggest that vitamin C pretreatment could protect mice from LPS-induced cognitive impairment, possibly through the modulation of oxidative stress and inflammatory responses.

REVIEW OF LITERATURE:

The pathogenesis of Covid -19 is due to virus-induced excessive immune reaction in the host. The activated leucocytes in the host produces a high level of pro inflammatory cytokines (mainly IL-6) and chemokines in circulation, which is labelled as “cytokine storm syndrome” (or Hyper cytokinemia) and it causes extensive tissue

Damages. Recently, few study states that, there is a catastrophic microvascular injury (endotheliitis) mediated by terminal complement components C5b-9 (membrane attack complex) and associated pro-coagulant state lead to thrombotic vasculopathy. Currently, covid-19 management is limited to symptomatic and palliative treatment. No therapies have been demonstrated to prevent the progression of covid-19 to severe illness, but several drugs are under trail. One of the promising drug is vitamin C or Ascorbic acid.

The decline in brain function associated with disease and old age could be due to the decline in the function of immune cells, which is likely caused by infection. As described in New Scientist, prompted by studies suggesting immune responses can help repair the nervous system, Jonathan Kipnis and colleagues at the University of Virginia created mice that lack CD4 cells, a kind of T-cell. They found the mice performed extremely poorly in tasks involving learning and memory, but when they were injected with CD4 cells from

healthy mice, their memories improved. Similarly, when he killed CD4 cells in healthy mice, their memory declined. Further animal studies by Kipnis and others show that learning new tasks triggers a mild stress response within the brain, which prompts CD4 cells to rally to the meninges, the membranes that surround the brain. Here, they release IL-4, which both switches off the stress response and tells brain cells called astrocytes to release brain-derived neurotrophic factor, a protein that enhances learning. Whether these animal studies are relevant to human learning and memory remains unclear, but there is some indirect evidence to support it.

Organs such as the brain are particularly resilient to vitamin C depletion due to ascorbate being recycled by glutathione in astrocytes through the pentose phosphate pathway. As plasma concentrations decline, more ascorbate is pumped into the cerebral spinal fluid in order to maintain homeostasis. Duration of deficiency has been shown to influence brain ascorbate concentrations to a higher degree than the amount of depletion. This is exemplified by observations in acute scurvy where brain concentrations of ascorbate are maintained through depletion of peripheral tissues, whereas marginal deficiency for longer periods of time has shown greater brain ascorbate depletions (27% depletion in 14 days in guinea pig brain tissue)

The brain's ability to recycle vitamin C and neurological symptoms that present from vitamin C deficiencies are reflections of the importance that the vitamin plays in central nervous functioning. Ascorbic acid acts as a cofactor in the synthesis of neurotransmitters, particularly of catecholamines-dopamine and norepinephrine. Vitamin C is suggested to influence this process via modulating the binding of neurotransmitters to receptors and regulating their release. Vitamin C is also a cofactor for tryptophan-5-hydroxylase required for the conversion of tryptophan to 5-hydroxytryptophan in serotonin production. Vitamin C deficiency has shown to decrease serotonin metabolites in both the cortex and striatum.

Moreover, ascorbic acid modulates the activity of excitatory receptors such as *N*-methyl-D-aspartate as well as inhibitory receptors such as aminobutyric acid (GABA) and inhibits the binding of glutamate to the NMDA receptor, thus demonstrating a direct effect in preventing glutamate excitotoxicity which causes neuronal dysfunction and degeneration.

Additionally, vitamin C has been shown to be involved in the biosynthesis of L-carnitine playing a role in the transport of fatty acids into mitochondria for energy production. Enzymes can readily convert carnitine to acetyl-carnitine and vice versa, according to the metabolic needs of the cell. Acetyl-carnitine can cross the blood brain barrier and act as a precursor in the production of acetylcholine and supports healthy cerebral blood flow.

Vitamin C also plays a role in the modulation of neuronal metabolism by changing the preference for lactate over glucose as the primary energy source in neurons sustaining synaptic activity. Ascorbate-dependent collagen synthesis has also been linked to the formation of myelin sheaths and regeneration of damaged sheaths that surround many nerve fibers. Ascorbic acid acts directly by scavenging reactive oxygen and nitrogen species produced during cell metabolism, and further recycles vitamin E involved in cell membrane integrity. Additionally, vitamin C has been found to induce the expression of brain derived neurotrophic factor (BDNF) – a component of several survival pathways. While blood samples are a more reliable measure of vitamin C status than self-reported vitamin C intakes, many factors can contribute to the instability of ascorbic acid in biological samples such as heat, light, and elevated pH (acidity).

RESULTS:

150 Covid-19 positive patients with neuro-cognitive impairment on admission studied and the following are the observation and analysis

TABLE 1: Age distribution n=150

Age Group	Number of Patients	Percentage
≤ 30 yrs	26	18%
31-40 yrs	51	34%
41-50 yrs	30	25%
51-60 yrs	33	23%

TABLE 2: Sex distribution

Sex	No of Patients	Percentage
Male	93	62%
Female	57	38%

Table 3 Neuro cognitive symptoms

Symptoms	Percentage
Cognitive dysfunction	82%
Head ache	68%
Numbness or tingling	52%
Loss of taste	58%
Loss of smell	64%
Muscle pain	88%
dizziness	42%
Blurred vision	24%
Tinnitus	18%
Non specific pains	12%
Fatigue	77%
Depression or anxiety	64%
Abdominal discomfort	45%

TABLE 4: Days on Neuro cognitive function recovery :

No of days	Percentage
<5 days	74%
>10days	26%

**TABLE 5: Age Wise Neuro cognitive function recovery :
LESS THAN 5 DAYS**

Age	Age Wise Percentage
<30 Years	90
31-40 Years	84
41-50 Years	72
51-60 Years	65

This study included 150 Covid-19 affected patients. As shown in Table 1, majority of the patients belong to the age group of 31-40 years. The minimum age was 20 years and maximum was 60 years. As shown in Table 2 ,most of the patients having Covid-19 were male (61%).This male predominance may have happened due to increased travel by males. In our study the common clinical manifestations are attention deficit and immediate recall memory.All the patients were subjected to mini mental score was done on 5th and 10th day of admission. As shown in Table 4, test results were confirmed in 74% of patients the improvement on 5th day and 26 % patients before 10 th day.The patients treated with high-dose oral liposomal vitamin C had increased rate of recovery from cognitive dysfunction . So, this result brings ray of hope in treating Covid-19 patients. 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, we require large scale multi centric clinical trials on high-dose oral liposomal vitamin C for creating standard treatment protocols for Covid-19 patients.

DISCUSSION:

The present study was devised with the aim of exploring whether there is an association between high dose oral liposomal vitamin C concentrations and cognitive function in cognitively intact adults, using paper and pen. We hypothesized that there would be a positive correlation between vitamin C and cognitive performance and that those administered high doser vitamin C concentrations would demonstrate higher cognitive performance than others.

As studied over the Neurological clinical presentations majority of our participants had cognitive dysfunction, followed by head ache,with varied age groups. The recovery rate was better among younger age group ,also significantly the outcome was good among the increased age group population. Normally increased age is associated with immune suppressed state and co morbidities plays slower recovery rate, but our elderly study participants showed significant recovery in the tests conducted at 5 th day of study period. This can be attributed to the liposomalized vitamin C with higher absorption rate and increases vitamin C in the bloodlevel which in turn modulates the neuro transmitters and neuro metabolism positively towards the improvement of cognitive functions as discussed earlier. Although the study did not aim to explain why some patients develop delayed recovery it suggests autoimmune mechanisms may be the play.

Globally various studies were conducted, in one of the studies the researchers tracked 50 long-haul COVID-19 patients who had laboratory-positive tests and 50 with lab-negative tests, although all met the definition of COVID-19 by criteria set by the Infectious Diseases Society of America, Korálnik said study participants resided in 21 states. Fifty-two were seen in-person and 48 by telehealth at a neuro COVID-19 clinic. They had either limited or comprehensive cognitive testing; memory and attention deficit problems were common. Many patients (42%) reported depression or anxiety prior to COVID diagnosis, said Korálnik, suggesting a "neuropsychiatric vulnerability" to developing long-haul COVID-19. Although the study did not aim to explain why some patients develop long-haul COVID-19, it suggests autoimmune mechanisms may be at play. The range of symptoms varied widely, with some patients experiencing cognitive impairment and dizziness, with no smell or taste issues, or vice versa, said Korálnik. Predicting recovery from specific symptoms is not yet possible. People tend to improve over time, but they do it at their own pace. We were hoping the further away from the disease onset, the better the patient would feel recovered. In fact that was not the case," said Korálnik. Some said, for instance, they were 95% recovered after 2 months, while others said they were only 10% recovered after 9 months. That means it is impossible to tell a patient with specific symptoms to expect recovery after a specific period of time

CONCLUSION:

The Covid-19 is rapidly increasing across the world at a frightening rate. Currently, there is no targeted antiviral medications available to fight against the disease. Hence, the present treatment strategy of symptomatic and supportive management is still the main treatment of covid-19. Accordingly, the high dose of oral liposomal vitamin C is recommended to use as an adjunct therapy to combat neuro cognitive dysfunction in covid-19 infection, with other supportive medications with better outcomes in all age groups with significant improvement in short duration. However, the most effective way to avoid covid-19 still remains frequent hand washing with soap for at least 20 seconds, use of hand sanitizers of at least 70% alcohol, covering cough and sneeze, not touching the eyes, nose or mouth, social distancing, universal face mask and keeping clean and disinfect frequently touched surfaces are the key in preventing the spread of infections.

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

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