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Research Article

The Potential Outcomes of Anti-Oxidant-4 Nutrients Cocktail in Covid-19 Associated Hyper-Oxidative Stress Status

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Abstract: Around 2 million individuals all over the globe are infected with the novel coronavirus 2019 that has emerged from Wuhan, China. It has rapid spreading rate by small droplets coming from sneezing or coughing of infected individual or asymptomatic carrier individual. The current management strategy is supportive; mainly hemodynamic and respiratory support. Fatalities are caused by severe pneumonia, sepsis, multi-organ failure, respiratory arrest and heart attack. Recent COVID-19 reports suggest a relation between hyper oxidative stress, caused by viral infection generally and heme dissociation particularly, and increased clinical deterioration of the patients. Patients suffers from cytokine storm and hyper-inflammatory status. In addition, they might be suffering from free heme accumulation and radical storm. Symptomatic and supportive treatments are needed at the same time side by side.). There are a lot of research and clinical trial to find a treatment or vaccine for this pandemic and only some of them were applied in clinical practice. Adjuvant micronutrients support is expected to decrease the oxidative stress status in these patients especially critically ill. Micronutrients includes vitamins C, A, E and trace element selenium are known for their anti-inflammatory and anti-oxidant effect.Through this review article, we highlight potential effect of use of antioxidant-4 cocktail COVID-19 infected patients.

Keywords: Hyper-Oxidative Stress Status, vitamin A, vitamin C, vitamin E, selenium, anti-oxidant, Radical Storm,COVID19.

INTRODUCTION

The fight against COVID-19 is still ongoing and new clinical findings are arising. Recently reported that the virus has proteins that can attack the porphyrin and heme group beside the previous findings of dysregulated production of inflammatory mediators leading to cytokine storm. Reviewing the viral life cycle shows that it attacks the respiratory system in particular the alveoli then replicates in them. Mature viruses are released and distribute all over our respiration. Alveolar cells are damaged and dissociation of hemoglobin occur. Both scenarios leads to impaired oxygenation and hypoxemia resulting in respiratory failure and weakens the patient condition further more. Hemoglobin destruction leads to disrupted oxygen distribution to tissue and carbon-dioxide removal. Free heme accumulates in blood leading to monocyte increased scavenging effect and more release of oxygen reactive species ROS that creates further tissue damage and end up with severe oxidative stress status.

Coronavirus disrupts the normal metabolic process of hemoglobin. Heme and globin are the main 2 components of hemoglobin. Once hemoglobin catabolism occur result into insoluble heme that binds to heme binding proteins and porphyrin excreted as bilirubin. The free iron released can be reused by the body, but if the resultant free iron exceeds the reutilization rate, this will result in iron overload and more production of ROS. Coronavirus contain proteins of orf1ab, ORF7a, and ORF8 that bind the heme and ORF10, ORF1ab and ORF3a attacks the heme to form a porphyrin. Those were the results of a study titled "COVID-19 Attacks the 1-Beta Chain of Hemoglobin and Captures the Porphyrin to Inhibit Human Heme Metabolism". Also, it has found a correlation between individuals with higher hemoglobin levels has a higher COVID-19 susceptibility. A recent study investigated the hemoglobin level in COVID-19 patients and found that hemoglobin is lowered significantly in patients with severe disease than patients with milder one.

Huge panic of high deaths and cases around the world lead to have enormous scientific race to find treatment or prophylaxis, depending on previous treatments like anti-viral and anti-microbial agents' and

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try to proof effectiveness in infected hospitalized patient .One of the new agent to be studied is antioxidant can decrease oxidative stress by direct scavenging of ROS .Ascorbic acid Vitamin C hydrophilic antioxidant that work as antioxidant and also enhance the immune response and blocking the formation of nitrosamines. α-tocopherol Vitamin E is the most potent lipophilic antioxidant that have antioxidant effect and it increasing humoral antibody protection and inhibition of mutagen formation . Selenium antioxidant that reduce both infection, oxidative stress and also protect against asthma. All antioxidant protect our body from damaging compounds called free radicals like iron, hydrogen peroxide, nitric oxide. Antioxidants preventing many human diseases such as: cancer, atherosclerosis, stroke, rheumatoid arthritis.

DISCUSSION

Viral and bacterial infection are associated with increased level of oxidative stress in lung tissue which caused lung injury by direct invasion of the virus and indirect hyperinflammatory status condition that result from the massive elevation in the levels of proinflammatory cytokines and chemokines reported in the infected patients. On the expense of maintaining oxygen delivery to the lung, this protocol carry the risk of hyperoxia -induced acute inflammatory lung injury (HALI). The typical picture of HALI appears as alveolar damage with increase in their capillary permeability, lung edema and leukocytes infiltration. The underlying pathogenesis of HALI can be explored as follow; the persistent hyperoxia increase lung mitochondrial electron chains and NADPH oxidases production of ROS including superoxide. This ROS are strong oxidizing agents that cause alveolar macrophages mediated phagocytosis dysfunction by two major mechanisms; oxidation of macrophages actin cytoskeleton and increase lung levels of high mobility group box 1 protein (HMGB1). This phagocytic dysfunction decrease the clearance efficacy of harmful invaders, thus increase the susceptibility to infections further complicating the condition.

Hepatic injury in COVID-19 infected patients has also been encountered, as clinical findings showed elevated serum levels of ALT, AST, LD, ALP, GGT, total and direct bilirubin with simultaneous decrease in albumin levels. Multiorgan damage especially lung and hepatic injury can be correlated to both hyperinflammatory and hyperoxidative status in COVID-19 patients. Deeply regarding " oxidant storm – hyperoxidative status" theory, what really happen can be summarized as follow; COVID-19 virus attack hemoglobin ß- chains releasing iron to the blood causing iron overload. Free iron as strong oxidizing agent pose sever harmful effects and mediate multiorgan failure. To capture this free iron and hinder its devastating damage, protective mechanisms are switched on, including (1) increase serum level of ferritin as major iron storing protein and positive acute phase reactant (2) increase in monocytes maturation to macrophages that regulate iron metabolism. Both manifestations have been documented by clinical results in COVID-19 patients.

Starting with Ascorbic acid vitamin C which is the nonenzymatic hydrophilic antioxidant, improves macrophages mediated phagocytosis and preservation of lung function, lung integrity by increased the resistance of chick embryo tracheal organ cultures to infection that occur in related to an avian coronavirus, on the other hand it has high susceptibility to various bacterial and viral infections .This can be attributed to the documented decrease in neutrophils infiltration, lung levels of HMGB1 and total lung protein content TLBC -as higher TLBC reflect higher lung injury severity - with a combined increase in ORP (oxidative reduction potential)of macrophages as sufficient vitamin C stores in these cells is crucial to maintain the reduction capacity of oxidants. Moving to AA role in acetaminophen APAP intoxicated hepatocytes; in vitro hepatocytes culture exposed to toxic dose of APAP caused decrease in mitochondrial activity, cellular proliferation almost to half, increase serum levels of liver enzymes(AST, ALT, ALP) and antioxidant enzymes (SOD, GSH, MDA). The administration of oral AA with different doses showed positive outcomes as demonstrated with enhancement of mitochondrial activity and cellular proliferation with diminished serum levels of liver and antioxidant enzymes. Such hepatoprotective outcomes have been also seen with α-tocopherol.

Vitamin E is a fat soluble vitamin is a strong scavenger of free radicals. vitamin E present in multiple isoforms as α-tocopherol pose anti-inflammatory effect while γ-tocopherol pose proinflammatory one with ROS scavenging for both. So the provision of pure α isoform is critical to obtain the desired outcomes. Liver preferentially retain α-tocopherol in body tissues with 10x compared to other isoforms due to the production of α-tocopherol transfer protein. During lipid oxidation, α-tocopherol will be consumed to scavenge the released ROS and then recycled back to the active reduced form with the assistance of vitamin C. Thus the availability of it is essential to prevent the accumulation of the oxidized tocopheroxyl that is by itself a damaging oxidant. it has an immune-modulatory effect seen in animal and human experimental models under disease condition. It enhances innate and adaptive immune responses. These immune-modulatory effects makes it a choice for immunity infection control.

Regarding selenium supplementation, it may have crucial beneficial effects on immunity.Glutathione peroxidases prevents oxidative cellular damage. Five selenium dependent glutathione peroxidase isoforms is discovered in human body. Another enzymatic system important for oxidative state regulation is thioredoxin

system. Selenium is an important cofactor in oxidative stress termination enzymatic systems. Interesting study has addressed the potential protective effect of selenium post- treatment to paraquat intoxicated patients. Paraquat is aggressive pulmonary toxin herbicide that mediate its damaging effect by promote the formation of superoxide as ROS. This lung damage was manifested as decrease in glutathione peroxidase activity, increase malondialdehyde levels with confirmed histological findings. The supplementation of selenium as antioxidant showed productive results listed as enhanced glutathione peroxidase function, attenuated lipid oxidation thus ROS release and overall decrease in lung injury score. Selenium appears to be important for immunity beyond its anti-oxidant effects. Nowadays, selenium is considered as essential microelement for human health.

Vitamin A is a fat soluble vitamin. Pro-vitamin A, which is B-carotene, is partly converted to vitamin A in small intestine, adipose tissue and macrophages. It is reported in literature that vitamin A has anti-infective and immuno-modulatory effect. During pathological process ROS is released and carotenoids beneficial anti-oxidant effect mainly of ROS scavengers. It works as chain breaking anti-oxidant. Carotenoids intake prevent many cancers and diseases due its anti-oxidant effect. B-carotene structure of conjugated carbon-carbon bonds system makes it efficient as anti-oxidant and radical scavenger. It has a unique structure and cleavage efficacy. Vitamin A deficiency causes increased mortality of infectious diseases. Pro-vitamin A, B-carotene has the strongest pro-vitamin A activity among other carotenoids. In addition it is well tolerated and do not cause hypervitaminosis A even when administered in up to 3000 RAE dose. Preclinical data collected from study conducted on rats exposed to monocrotaline showed hepato and pulmonary protective effects of ß-carotene. Monocrotaline is pyrrolizidine alkaloid that exert its toxicity after being activated by liver metabolism by causing DNA-DNA DNA- protein cross linking and oxidative stress. The hepatotoxicity was clearly documented by hepatic hemorrhage, fatty infiltration and cell necrosis, while pulmonary toxicity manifested as interstitial edema, inflammation, bleeding and fibrosis. And the introduction of ß-carotene has successfully reverse the toxicity signs.

The safety and effectiveness of vitamins and trace elements need further elucidation. Micronutrients are important for immune system integrity including vitamin C, A, E, D, B12, and trace elements of selenium and zinc. After reviewing literature, the potential outcomes of the four nutrients can be described as reducing harmful effects from ROS and iron overload, possible immunity enhancing effect, decrease risk for organ failure, reduce ICU stay and mechanical ventilation use and improve quality of life of COVID-19 infected patients.

CONCLUSION

In summary, Imbalance between reactive oxygen species formation and insufficient anti-oxidant defense system results in oxidative stress. Vitamin A, C E and selenium can trap and neutralize free radicals. Vitamins and trace elements play an important role in maintaining the homeostasis of the human body, prevent hyper-oxidative status damage and some immune enhancing effects. In our review article, we suggest the adoption of antioxidant-4 cocktail as promising management protocol in COVID-19 infected people based on the homology of its pathogenesis with other oxidative stress conditions and the documented preclinical usefulness. We also recommend that future clinical studies to be carried out to standardize the therapy and evaluate its safety and efficacy in COVID-19 cases.

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