

Research Article

N-Acetyl Cysteine Infusion as a Proposed Reactive Oxygen Species Combater in SARS-COV-2 in Infected Critically Ill Patients with Hyper-Oxidative Stress Status

"Moh'd Nour" Mahmoud Bani Younes; Ph¹, Amani Daoud Alshawabkeh; PharmD¹, Tala Tayseer Malhis; PharmD², Haneen Nawaf AL-Sabbah; PharmD², Zahraa Gh.A. Alameri; PharmD²

¹Clinical Pharmacy Department, King Hussein Medical Hospital, Royal Medical Services, Amman, Jordan

²Clinical Pharmacy Department, The University of Jordan, Amman, Jordan

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Abstract: The Coronavirus disease 2019 (COVID-19) has been a global outbreak and emergency declared by the WHO. Yet no conformed vaccine or drug that will end this pandemic crisis as it takes months if not years to develop as well as it is costly and the process to deliver the drug to the whole world is long while people are dying from the deadly virus. The hyper-oxidative stress that resulted from the pathogenesis of SARS-CoV-2 leads to detrimental consequences and multiple organ failures that lead to sudden death. As it's evident from the free radical theory, the release of oxidative iron from hemoglobin overwhelms the natural detoxifying mechanisms leading to prolonged and persistent hypoxia. Antioxidants like N-Acetyl cysteine are suggested as a viable therapeutic approach for attenuating tissue damage induced by oxidative stress. An overreaction of the immune system will develop as a form of systemic inflammatory response, which is called a cytokine storm. Unlike free radical theory, cytokine storm theory may not always lead to multiorgan failures and death. This emphasizes the seriousness of free radical theory and the promising role of antioxidant use in SARS-COV-2 in infected critically ill patients. Therapeutic infusion of N-Acetyl cysteine will increase the levels of glutathione which counteracts the catastrophic action of free radicals by boosting cellular defense against oxidative stress.

Keywords: Antioxidants; Critically Ill Patients; Hyper-Oxidative Stress Status; N-Acetyl cysteine; Radical Storm; Reactive Oxygen Species; SARS-COV-2.

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INTRODUCTION

Respiratory infections are the leading cause of disease globally (Joseph, p. 2006). Nowadays coronavirus 2 (SARS-CoV-2) which cause respiratory infection known as COVID-19 is officially pandemic according to World Health Organization (World health organization, 2020). The virus is highly contagiousness and spreads rapidly according to center for disease control and prevention (Center for Disease Control and Prevation,2020). Coronavirus 2 (SARS-coV-2) targets the human respiratory system, resulting in symptoms after the incubation period. The most common symptoms at onset of COVID-19 illness are fever, cough, and fatigue, while other symptoms include sputum production, headache, hemoptysis, diarrhea, dyspnea, rhinorrhea, sneezing, sore throat and lymphopenia (Yi,Philip, *et al.*,2020).

Most patients with severe COVID-19 exhibit substantially elevated serum levels of pro-inflammatory cytokines including IL-6 and IL-1 β , as well as IL-2, IL-

8, IL-17, G-CSF, GM-CSF, IP10, MCP1, MIP1 α (also known as CCL3) and TNF, characterized as cytokine storm (Yaling ,S. *et al* .,2020) which had led to suggestion cytokine storm as a theory to explain the decrease PaO₂/FiO₂ ratio [the ratio between the blood pressure of the oxygen (partial pressure of oxygen, PaO₂) and the percentage of oxygen supplied [fraction of inspired oxygen, FiO₂]] < 300 that indicate Acute Respiratory Distress Syndrome (ARDS) (Marco, C.at el., 2020).On the other hand, PaO₂/FiO₂ ratio index does not correlate with Chest X-ray (TR,M. *et al.*, 2013). Moreover the theory does not explain many laboratories observation in COVID-19 patients including but excluded to; increase in Aspartate Aminotransferase (AST), Alanine Aminotransferase (ALT), Alkaline Phosphatase (ALP), total bilirubin and indirect bilirubin (Versa, *et al* .,2020). Also, increasing monocyte to lymphocyte ratio (MLR) that can be considered independent biomarkers for indicating poor clinical outcome (Ai-Ping,Y. *et al.*,2020).

A Meta-analysis shows that functional hemoglobin values are reduced in COVID-19 patients with severe disease (Giuseppe, L. *et al.* 2020). Coagulation abnormalities such as PT and aPTT prolongation and high ferritin level were noticed. Furthermore high percentage of COVID-19 patients with disseminated intravascular coagulation (DIC) (Journal of Thrombosis and Haemostasis, 2020). Another study showed that proteinuria, hematuria, and elevated levels of blood urea nitrogen, serum creatinine, uric acid as well as D-dimer were significantly that could develop to AKI and increases the mortality rate (Zhen, L., 2020). So those limitations in the cytokine storm theory emerged the need for another theory that matches those laboratories findings. And a suitable drug regimen that go along the new theory which is N-Acetyl cysteine.

DISCUSSION

Hyper oxidative stress theory has put things into perspective. A study showed that coronavirus 2 ORF8 and surface glycoprotein could bind to the porphyrin which is a heterocyclic ring holds heme group consist of an iron that form the hemoglobin the main component in red blood cells. At the same time, ORF1ab, ORF10, and ORF3a proteins could coordinate an attack on the 1-beta chain of hemoglobin to dissociate the iron. Hemolysis happens and the ability of hemoglobin to carry oxygen is lost. That's why we have reduced functional hemoglobin values in COVID-19 patients with severe disease. The lung cells have extremely intense poisoning and inflammatory due to the inability to exchange carbon dioxide and oxygen frequently, which eventually results in ground-glass-like lung images, we have seen in COVID-19 patients. The mechanism also interferes with the normal heme anabolic pathway of the human body (Wenzhong, L. *et al.*, 2020).

Iron can catalyze the conversion of hydrogen peroxide to free-radical ions that attack cellular membranes, protein and DNA (Jacques, *et al.*, 2001). This leads us to assuming a Radical Storm and Hyper Oxidative Stress condition inside COVID-19 patient body. The Oxidative Stress could be a possible pathogenic for ARDS (Bernard, B. 2000). This clarifies why we have high level of ferritin in COVID-19 patients as we mentioned. And reveal the reason for increase of monocytes in relative to lymphocytes in COVID-19 patients, the monocyte will differentiate to macrophages then phagocytosis happens to get rid of iron overload. As well as the cause of high bilirubin levels in blood. As we know heme is converted to bilirubin. A study finding that bilirubin could have radical scavenger activity (Sylvain, D., 1999). This goes along that patient is in hyper oxidative stress status.

N-Acetyl cysteine reacts with cystine, reducing it to cysteine and producing NAC-NAC and NAC-Cysteine. Therapeutic concentrations of NAC can

provide sufficient levels of cysteine by reduction of cystine, that supports and sustain normal GTH concentrations even in oxidatively stressed RBCs. Acetylcysteine with antioxidant effect is the best candidate for treating SARS-COV-2 infected critically ill patients with hyper Oxidative Stress Status. In acetaminophen toxicity NAPQI is formed, a reactive oxygen species (free radical), which is going to cause hepatic toxicity (Jack, H. *et al.* 2011). Acetylcysteine is an antioxidant common in clinics for acetaminophen toxicity antidote. With the elevated of laboratory parameters related to liver in COVID-19 patients, acetylcysteine is going to be a safe option that protects the liver from the radicals. Also serve as cysteine donor, suitable for cysteine/GSH deficiency (Kondala, R. 2007). It is capable of raising RBC glutathione level, reduced the number of days of acute lung injury (Gordon, B. *et al.*, 1997).

The hepatoprotective effect can be useful for patients with COVID-19 whose have elevated aminotransferases and bilirubin, accompanied by greater activation of coagulative and fibrinolytic pathways resulting in significant liver dysfunction (Bangash & Jaimin *et al* 2020).

NAC is likely safe, it provides protective benefit for patients with renal impairment, prevents contrast-induced nephropathy (CIN) and increase the protection capability of hepatic cell from free radicals. It's crucial to prevent the multi-organ failures that results from oxidative stress according to the free radical theory of COVID-19 by replenishing the antioxidants using N-acetyl cysteine. Moreover, it interrupts the formation of disulfide bonds in von Willebrand factor multimerization; a key event of the initiation of platelet aggregation (Junmei, C. *et al.* 2011). This will mitigate the hypercoagulable status the patient is suffering from and decrease the chance of DIC that comes with high mortality rate.

There are several N-Acetylcysteine doses we suggest for treatment COVID-19 patients. One suggestion is using N-Acetylcysteine dose that has the potential to treat β -thalassemia disease. This is convenient since Oxidative Stress and iron overload are the main pathophysiological mechanisms in thalassemia. We suggest the dose of 200 mg/day for adults and 10 mg/kg for children, since a clinical study of 60 participants adults treated with 200 mg/day N-Acetylcysteine and showed after 3 months significant decrease in iron toxicity, increase in functional hemoglobin/nonfunctional hemoglobin quotient, increase in GSH and improve coagulability status. Another proposal is IV NAC infusion regimen for 21 hours that used in treating Acetaminophen overdose. 21-hour regimen: Consists of 3 doses; total dose delivered: 300 mg/kg for adult or child. With **loading dose:** 150 mg/kg (maximum: 15 g) infused over 1 hour, **Second dose:** 50 mg/kg (maximum: 5 g) infused over 4

hours, **Third dose:** 100 mg/kg (maximum: 10 g) infused over 16 hours. Pharmacokinetically, N-Acetylcysteine crosses the placenta but for breast feeding it is unknown. Volume distribution is 47 L/kg and Protein binding is between 66% to 87%. As for the elimination $T_{1/2}$ in reduced acetylcysteine it is 2 hours and in total N-Acetylcysteine if Adults =5.6 hours but Newborns = 11 hours. Time to peak, plasma for Oral solution: 1 to 2 hours. And it is Excreted in Urine (13% to 38%) (UpToDate, 2020).

Most clinical trials have shown benign side effects from NAC including mild gastrointestinal side effects (nausea, vomiting, and diarrhea or constipation). Rarely, it can cause anaphylactic reactions including flushing, urticaria, bronchospasm, hypotension and angioedema when given intravenously at high doses (>3g/day) (Seetal, Olivia, *et al.*,2008). One-year treatment of β -thalassemia was safe since no abnormalities in hematological parameters, liver function, or renal function were observed. The severe side effects including agranulocytosis or neutropenia were not observed in any of the patients (Orn-uma, Y. *et al.* 2015). And a randomized control trial was conducted on 75 children with dose 10 mg/kg acetylcysteine also holds same positive outcomes (Zeynep, Ö. *et al.* 2014). N-Acetyl cysteine can be a potential therapeutic agent that can rescue SARS-coV-2 infected critically ill patients with Hyper-Oxidative Stress Status by its detoxifying role from free radicals. NAC can replenish glutathione in states of potential insufficiency that is found in COVID-19 infected patients .

CONCLUSION

In summary, the lab results of COVID-19 patients reveal that the patient is under oxidative stress status mainly by hemolysis of the red blood cells and iron overload. And there is a radical storm inside their body. N-Acetylcysteine is our proposal drug that could save patient life as it's available and not expensive. Through N-Acetylcysteine nature as antioxidant and radical scavenger, we assume it is going to protect liver, kidney of the patient, decrease the chance of acute respiratory distress syndrome or disseminated intravascular coagulation (DIC) and decrease the mortality rate for our patient. We suggest a randomized controlled clinical trial to test clinical usefulness of the N-Acetylcysteine in treating COVID-19 infected critically ill patient with Hyper-Oxidative Stress status.

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