EAS Journal of Anaesthesiology and Critical Care
Abbreviated Key Title: EAS J Anesthesiol Crit Care
ISSN: 2663-094X (Print) & ISSN: 2663-676X (Online)
Published By East African Scholars Publisher, Kenya

OPEN ACCESS

Volume-2 | Issue-2 | Mar-Apr-2020 | DOI: 10.36349/easjacc.2020.v02i02.004

Research Article

Desferrioxamine Contineous Infusion with Adjunctive Packed Red Blood Cells as an "Iron Overload-Hyperoxidative Status-Radical Storm" Management Strategy in Late Stage Covid-19 Infected Critically Ill Patients

"Moh'd Nour" Mahmoud Bani Younes; Ph, Jaafar Abd Alrahman Abu Abeeleh; Ph[1], Raghad Mohammad Daknash; Pharm D[2], Ameera Rasmi Noufal; PharmD[2] & Zahra Amjad AL-Masalha; PharmD[2]

[1]Clinical Pharmacy Department, King Hussein Medical Hospital, Royal Medical Services, Amman, Jordan
[2]Clinical Pharmacy Department, The University of Jordan, Amman, Jordan

Article History
Received: 11.03.2020
Accepted: 13.04.2020
Published: 19.04.2020

Journal homepage:
https://www.easpublisher.com/easjacc

Quick Response Code

Abstract: As of April 13, 2020, A novel coronavirus, also known as COVID-19 or SARS-CoV-2 has been confirmed in 1,858,800 people worldwide, carrying a mortality of approximately 3.4%. As COVID-19 cases increase day by day, scientists are digging to reveal all about this pandemic virus, and many drug suggestions have been under clinical trials to decrease the mortality based on the theory of " cytokine storm- hyperinflammatory status". However new researches and studies have discovered that the reactive oxygen species (ROS) storm instead of cytokine storm is the primary pathogenesis cascade that contributes to the exponential mortality pattern in in late stage COVID-19 infected critically ill patients. The impact of COVID-19 on the health, economic and political systems made it a hot topic for research. Therefore, new drug ideas that deals with the underlining contributors of the disease are needed. In this review article, we aim to introduce a novel management strategy using continuous Desferrioxamine (an iron chelating agent) infusion with adjunctive PRBCs based on the new theory of the disease pathogenesis named as "Iron overload-hyperoxidative status-radical storm" and the extrapolation of the clinical outcomes of this strategy in blood transfusion dependent thalassemia.

Keywords: Critically ill patients; Desferrioxamine; Hyperoxidative status; Late stage COVID-19; Iron overload; Radical storm; Packed RBCs.

INTRODUCTION

The novel coronavirus pneumonia (COVID-19) is a contagious acute respiratory infectious disease usually associated with fever, and the temperature above 38 degrees with symptoms such as dry cough, fatigue, dyspnea, difficulty breathing, and frost-glass-like symptoms in the lungs (Huang *et al.*, 2020). In order to provide the best management for the infected patient, exploring the underlying pathology is highly important. For a while, the most accepted pathogenesis was believed to be due to cytokine storm that cause hyperinflammatory state and multi organ failure. This has been supported by clinical findings that showed huge elevation in the level of proinflammatory cytokines including, IL-6, IL-12, IL-18, etc. and chemokines including CCL2, CCL3, CXCL9, etc. The pathophysiology of COVID-19 and the contribution of cytokine storm and pro-inflammatory mediators in the mortality has been widely discussed, despite the management of critically ill patients and the measures taken to maintain airways, number of deaths are still increasing day by day, as overall deaths have crossed a 100 thousand as of 12th April 2020.(Worldometer, 2020). Accordingly, the cornerstone of the management relay on respiratory support to deliver oxygen using face mask, high flow nasal cannula, mechanical ventilation, and extracorporeal membrane oxygen support as needed.

Although of the provision of the practiced supportive care, some cases go to poor prognosis and even death. And here the question arises that maybe the theory on which the practice has been built on do not provide the full picture of the pathogenesis. Last updates regarding COVID-19 pathogenesis suggests that that cytokine storm syndrome (C. Chen *et al.*, 2020) and the high level of oxidative iron-ferritin lead to state of hyper oxidative stress condition. Hence it is not surprising to know that the pathogenesis of COVID-19 has gone far beyond the cytokine storm and the resulting ARDS, it is not only a regular virus that attacks the respiratory system and damages it, but also involves systemic multi-organ damage, as this virus

***Corresponding Author**: "Moh'd Nour" Mahmoud Bani Younes **Email**: panasomycine@hotmail.com

does not only infect the epithelial cells of the lung but also has succeeded to invade RBCs, liver, neural tissues, Gastrointestinal tract and causes coagulopathy (Ribeiro *et al.,* 2020). A new theory defined as " radical storm – hyperoxidative status " proposed that the pathogenesis maybe due to RBCs invasion by the virus. COVID-19 is a positive-strand RNA virus could attack the ß chain of hemoglobin (Hgb) releasing iron to the blood causing iron overload. This iron overload pose harmful effects on the body as iron is a strong oxidizing agent (Wu *et al.,* 2020). This in turn trigger compensatory protective mechanisms to reduce its toxicity. These compensatory mechanisms including but not excluded to increase in serum ferritin level, hyper-production of new RBCs, and monocytosis.

There are many consequences and negative impacts that resulted from these compensatory mechanisms. Firstly, the involvement of RBCs, it was discovered that COVID-19 causes porphyria (increased amount of porphyrin), that happens as the virus attacks the β 1-Hgb resulting in iron detachment from heme moiety, thus decreasing the functional/nonfunctional Hgb ratio that resulting in refractory hypoxia that do not respond to respiratory supportive care, hyperproduction of new RBCs, unconjugated bilirubin elevation, and blood hyperviscosity/hypertension status . In case of COVID-19 infection, the rate of iron release exceeds the capacity of the protective mechanisms, exposing the body to iron toxicity that will stimulate monocytes in an excessive manner, increase C-reactive protein to albumin ratio (CRP: ALB), increase ferritin level which will place the body in severe stress condition. Cells react to stress due to inflammation, producing large amounts of serum ferritin to bind free iron ions to reduce damage. That was noticed after biochemical examination indexes of 99 patients with novel coronavirus pneumonia, and the report also reflected the abnormal phenomenon of hemoglobin-related biochemical indexes of patients (N. Chen *et al.,* 2020). It is noted that the COVID-19 has succeeded to dissociates and replace the iron from the heme ring via its surface glycoproteins that covers it's envelop which are ORF8, ORF10 and ORF3a (W. Liu & Li, n.d.). A special feature about COVID-19 that it is opposite to other viral infection in the elevation of lymphocytes, in this virus most of the patients have shown lymphopenia, and increase in monocytes which is misleading to the over prescription of unneeded antibiotics. Since there is an increased rate of RBCs rupture and release of iron, monocytes play a vital role in iron homeostasis and decrease iron toxicity by a process called erythrophagocytosis (Tan *et al.,* 2020; Haschka *et al.,* 2019; & Zhou *et al.,* 2020).

Secondly, the liver involvement, it is a critical issue in patients with severe case of COVID-19, clinical studies have shown that many patients has expressed liver comorbidities and increase in the level of alanine aminotransferase (ALT), aspartate aminotransferase (AST), Alkaline phosphatase, lactate dehydrogenase (LDH), and total bilirubin, but it is noteworthy to mention that liver damage is not caused by direct invasion of the virus to hepatocytes but due to inflammation all over the body that is the result of increased free iron level that exacerbate leukocytosis specially macrophages. (C. Liu *et al.,* 2020; &Zhang *et al.,* 2020). Thirdly, the interference of COVID-19 with coagulation cascade, which results in disseminated intravascular coagulation (DIC) and platelets dysfunction that resulting in resulting in elevation of D-dimer, prothrombin time (PT), activated partial thromboplastin time (aPPT), and bleeding risk. DIC tends to occur at day four and mostly found in patients who didn't survive the disease and its manifestations include low platelets count and increased D-dimer. DIC doesn't only happens due to the cytokine storm but also due to radical storm-hyperoxidative stress status that eventually leads to death (Thachil *et al.,* 2020). Four issue regarding COVID-19 pathogenesis. Fourthly, the lung injury as supported by chest CT, which shows a bilateral ground glass and consolidation opacities, in addition to low PaO2/FiO2 ratio associated refractory hypoxia.

The dissociation of iron from hemoglobin leads to RBCs early and frequent lysis which resembles thalassemia in its pathogenesis as pallor, jaundice, liver cirrhosis and fibrosis, dilated cardiomyopathy, venous thrombosis, endocrine glands abnormality, fatigue and importantly shortness of breath and decrease in O2 saturation leading to pulmonary hypertension.(Galanello & Origa, 2010),(De Castro, Jonassaint, Graham, Ashley-koch, & Telen, 2004). Thalassemia major is a heredity disease causing diminished ability to produce functional Hgb. The abnormal morphology of the RBCs leads to premature hemolysis and excessive iron release causing iron overload. The first line management of transfusion – dependent thalassemia is RBCs transfusion to maintain tissue oxygenation in combination with desferrioxamine as iron chelator to avoid iron overload toxicity. This therapeutic approach demonstrates its safety and efficacy as it has been widely implanted in clinical practice since long time. Accordingly, we can extrapolate the clinical outcomes obtained from the application of this approach in transfusion – dependent thalassemia patients on COVID-19 infected ones.

DISCUSSION

According to the latest observations in post-mortem COVID-19 infected patients and autopsy of corona's dead patients, the signs of iron overload and DIC are main cause of COVID-19 mortality not ARDS. The emergence of the new "Radical storm – Hyperoxidative status" theory give better and more logical explanations of the clinical findings seen in COVID-19 infected patients including, elevation in serum ferritin, monocyte count, D-dimer, liver enzymes among others. And highlight the reason behind the

refractory hypoxia seen despite the respiratory supportive care provided. ARDS seen in the patients is mainly due to two causes. Firstly, the invasion of the lung alveoli with the virus mediated by its attachment at ACE2. Secondly, the invasion of the RBCs with the virus liberating the iron which pose more lung damage and further decrease in pulmonary function. The shift of the underlying proposed pathogenesis theory from "Cytokine storm- Hyperinflammatory status" to " Radical storm – Hyperoxidative status " necessitate the shift to or at least the addition of new management approach. Since the aforementioned pathogenesis of COVID-19 is strongly correlated to toxicity of free iron and based on the homology of the pathological picture of COVID-19 and thalassemia major, the proposal of desferrioxamine for the management of severe cases of COVID-19 combined with packed RBCs is of reasonable value.

The mechanism of action of desferrioxamine is an iron-chelating agent that forms a stable water-soluble complex with iron that is excreted via the kidney or feces and has a relatively high molecular weight of 560.7 g/mol which makes it hard to penetrate tissue and cause adverse effects. Due to its molecular size, desferrioxamine is poorly absorbed from the gut. The higher the dose, the higher the proportion of iron excreted in the faeces rather than the urine. Moving to the pharmacokinetics and pharmacodynamics of this drug, clinical trials has shown that β-thalassemia patients have received 50 mg/kg/d as continuous infusion with an initial half-life of 0.28 hr and Css average of 7 micromol/L. Desferrioxamine has a short plasma half-life, being eliminated rapidly in urine and bile. The process of iron chelation ceases soon after an infusion of desferrioxamine is complete. The efficiency of desferrioxamine (measured in terms of percent of dose excreted in the iron bound form) administered at standard 8–12 hour intervals 5–7 days a week is approximately 14%. Iron excretion with desferrioxamine increases with dose, with body iron stores and in vitamin C deficient patients with the addition of vitamin C (McCance & Widdowson, 1938). A clinical trial has shown that the pharmacodynamics and efficacy of 24 hours continuous infusion of desferrioxamine is superior than IM injections due to higher plasma residency of the drug (Porter, 2001).

Moreover, it is of a crucial value to provide patients with functional RBCs to deliver the proper amount of oxygen to various tissues, therefore the idea of administering packed RBCs in combination desferrioxamine is to bypass the compensatory non-functional Hgb associated Hypers triad (Hgb Hyperproduction, Hyperviscosity, and Hypertension). To reduce the lysis of the transfused RBCs, it is important to screen for packed cells Rh to decrease the alloantibodies formation. A clinical trial has shown that co-administration of desferrioxamine with chronic packed RBCs has shown a significant decrease in pulmonary vascular resistance and plasma thrombin-antithrombin III complex (a marker of coagulation), also the idea of continuous infusion of desferrioxamine has come to reduce the potentiality of increasing iron toxicity from the transfused RBCs (Sadeghian *et al.*, 2009), (Atichartakarn, Chuncharunee, Chandanamattha, Likittanasombat, & Aryurachai, 2004).

To remain unbiased, it is important to mention both the advantages and side-effects of using desferrioxamine. To begin with the advantages, using this drug is not only to decrease free-iron load but also as conducted in a clinical trials performed on mice that is has neuroprotective role as COVID-19 was also found in CSF and has succeeded to cross the BBB, as it inhibits radical production and lipid peroxidation therefore decrease the hypoxic-ischemia in the brain and reduces the injury (Sarco, Becker, Palmer, Sheldon, & Ferriero, 2000). As desferrioxamine has a role in inhibiting lipid peroxidation, another trial performed on mice suggested the vital role of this drug in inhibition of iron-dependent OH-production due to its role in scavenging FE^{+2} thus decrease hepatotoxic effects, also a randomized clinical trials suggested the ability of this drug to largely decrease the liver-iron overload (Siegers, Steffen, & Younes, 1988; & Maggio *et al.*, 2002). A clinical trial has demonstrated the adverse events associated with the induction of iron-chelating agent which are, gastrointestinal discomfort, transient skin rash, fatigue, loss of appetite, nausea, joint pain and headache also a small number of patients suffered from serious side effects as agranulocytosis and neutropenia (Alymara *et al.*, 2004).

CONCLUSION

In summary, COVID-19 with its worldwide spreading and impact attract the research area toward the development of successful management protocol. It is necessary to demonstrate that cytokine storm is not the only contributor to death in severe cases of COVID-19, because despite measures taken to treat ARDS and the high percentage of provided O2, patients are still dying. Our novel approach using PRBCs transfusion with continuous desferrioxamine infusion pose a promising future in this field as the extrapolated safety and efficacy was obtained from long history clinical practice in transfusion – dependent thalassemia. Since COVID-19 death rates are increasing day by day, it is of interesting to investigate our proposed “Chelator-Replacer” strategy with clinical prospective studies for standardization and establishment of its safety and efficacy at least in late stage COVID-19 infected patients. Giving the patients iron chelating agent like desferrioxamine continuous infusion for 48 hours with adjunctive packed RBCs could reverse iron overload and reduce hypoxia associated mortality in this pandemic disease.

REFERENCES

1. Alymara, V., Bourantas, D., Chaidos, A., Bouranta, P., Gouva, M., Vassou, A., ... & Bourantas, K. L. (2004). Effectiveness and safety of combined iron-chelation therapy with deferoxamine and deferiprone. *The Hematology Journal*, *5*(6), 475-479.
2. Atichartakarn, V., Chuncharunee, S., Chandanamattha, P., Likittanasombat, K., & Aryurachai, K. (2004). Correction of hypercoagulability and amelioration of pulmonary arterial hypertension by chronic blood transfusion in an asplenic hemoglobin E/β-thalassemia patient. *Blood*, *103*(7), 2844–2846. https://doi.org/10.1182/blood-2003-09-3094.
3. Baig, A. M., Khaleeq, A., Ali, U., & Syeda, H. (2020). Evidence of the COVID-19 virus targeting the CNS: tissue distribution, host–virus interaction, and proposed neurotropic mechanisms. *ACS chemical neuroscience*.
4. Covid-19: acquired acute porphyria hypothesis. (n.d.). Retrieved April 13, (2020), from https://www.researchgate.net/publication/340462006_Covid-19_acquired_acute_porphyria_hypothesis
5. COVID-19: consider cytokine storm syndromes and immunosuppression - The Lancet. (n.d.). Retrieved April 1, (2020), from https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(20)30628-0/fulltext.
6. De Castro, L. M., Jonassaint, J. C., Graham, F. L., Ashley-koch, A., & Telen, M. J. (2004). Pulmonary Hypertension in SS, SC and Sβ Thalassemia: Prevalence, Associated Clinical Syndromes, and Mortality. *Blood*, *104*(11), 1663–1663. https://doi.org/10.1182/blood.v104.11.1663.1663.
7. Deferoxamine | C25H48N6O8 - PubChem. (n.d.). Retrieved April 13, (2020), from https://pubchem.ncbi.nlm.nih.gov/compound/Deferoxamine.
8. Galanello, R., & Origa, R. (2010, May 21). Beta-thalassemia. *Orphanet Journal of Rare Diseases*, *5*, pp. 1–15. https://doi.org/10.1186/1750-1172-5-11.
9. Haschka, D., Petzer, V., Kocher, F., Tschurtschenthaler, C., Schaefer, B., Seifert, M., … Tymoszuk, P. (2019). Classical and intermediate monocytes scavenge non-transferrin-bound iron and damaged erythrocytes. *JCI Insight*, *4*(8). https://doi.org/10.1172/jci.insight.98867.
10. Levi, M. (2007). Disseminated intravascular coagulation. *Critical care medicine*, *35*(9), 2191-2195.
11. Liu, C., Jiang, Z. C., Shao, C. X., Zhang, H. G., Yue, H. M., Chen, Z. H., … Qi, X. L. (2020). [Preliminary study of the relationship between novel coronavirus pneumonia and liver function damage: a multicenter study]. Zhonghua Gan Zang Bing Za Zhi = Zhonghua Ganzangbing Zazhi = Chinese Journal of Hepatology, 28(2), 148–152. https://doi.org/10.3760/cma.j.issn.1007-3418.2020.02.003.
12. Liu, W., & Li, H. (2019, Dec). COVID-19: Attacks the 1-Beta Chain of Hemoglobin and Captures the Porphyrin to Inhibit Human Heme Metabolism.
13. Maggio, A., D'Amico, G., Morabito, A., Capra, M., Ciaccio, C., Cianciulli, P., … Midiri, M. (2002). Deferiprone versus deferoxamine in patients with thalassemia major: A randomized clinical trial. *Blood Cells, Molecules, and Diseases*, *28*(2), 196–208. https://doi.org/10.1006/bcmd.2002.0510.
14. Porter, J. B. (2001). Deferoxamine pharmacokinetics. *Seminars in Hematology*, *38*, 63–68. https://doi.org/10.1016/S0037-1963(01)90061-7.
15. Ribeiro, F., Bibi, M., Pereira, M., Ferreira, S., Pessegueiro, H., & Araújo, R. (2020). Severe Acute Liver Injury Related to Heat Stroke. 9–11. https://doi.org/10.12890/2020.
16. Sadeghian, M. H., Keramati, M. R., Badiei, Z., Ravarian, M., Ayatollahi, H., Rafatpanah, H., & Daluei, M. K. (2009). Alloimmunization among transfusion-dependent thalassemia patients. *Asian Journal of Transfusion Science*, *3*(2), 95–98. https://doi.org/10.4103/0973-6247.53884.
17. Sarco, D. P., Becker, J., Palmer, C., Sheldon, R. A., & Ferriero, D. M. (2000). The neuroprotective effect of deferoxamine in the hypoxic-ischemic immature mouse brain. *Neuroscience Letters*, *282*(1–2), 113–116. https://doi.org/10.1016/S0304-3940(00)00878-8.
18. Sci-Hub | High serum ferritin level as a marker of malignant histiocytosis and virus-associated hemophagocytic syndrome. *Cancer*, *61*(10), 2071–2076 | 10.1002/1097-0142(19880515)61:10<2071::AID-CNCR2820611023>3.0.CO;2-6. (n.d.). Retrieved April 13, 2020, from https://sci-hub.tw/https://doi.org/10.1002/1097-0142(19880515)61:10%3C2071::AID-CNCR2820611023%3E3.0.CO;2-6.
19. Siegers, C. P., Steffen, B., & Younes, M. (1988). Antidotal effects of deferrioxamine in experimental liver injury - role of lipid peroxidation. *Pharmacological Research Communications*, *20*(4), 337–343. https://doi.org/10.1016/S0031-6989(88)80070-5.
20. Tan, L., Wang, Q., Zhang, D., Ding, J., Huang, Q., Tang, Y.-Q., … Miao, H. (2020). Lymphopenia predicts disease severity of COVID-19: a descriptive and predictive study. *Signal Transduction and Targeted Therapy*, *5*(1), 1–3. https://doi.org/10.1038/s41392-020-0148-4.
21. Thachil, J., Tang, N., Gando, S., Falanga, A., Cattaneo, M., Levi, M., … Iba, T. (2020). ISTH interim guidance on recognition and management of coagulopathy in COVID-19. *Journal of Thrombosis and Haemostasis*. https://doi.org/10.1111/jth.14810.
22. World o meter. (2020). Coronavirus Cases. https://doi.org/10.1101/2020.01.23.20018549V2

23. Zhang, C., Shi, L., & Wang, F. S. (2020). Liver injury in COVID-19: management and challenges. *The Lancet Gastroenterology and Hepatology*, 5(May), 428–430. https://doi.org/10.1016/S2468-1253(20)30057-1.
24. Zhou, F., Yu, T., Du, R., Fan, G., Liu, Y., Liu, Z., … Cao, B. (2020). Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. *The Lancet*, *395*(10229), 1054–1062. https://doi.org/10.1016/S0140-6736(20)30566-3.

Acknowledgement

I would like to thank my parents, whose love and guidance are with me in whatever I pursue. Most importantly, I wish to thank my loving and supportive wife, and my three wonderful children who provide unending inspiration. Also, I would like to express my gratitude to my PharmD students at The University of Jordan for their supporting in pursuing this minireview.

Conflicts of interest: None declared.

Funding: This work was supported by Aleiman Drug Store Company.