Archives of Anesthesiology and Critical Care (Summer 2024); 10(3): 232-238.

Available online at http://aacc.tums.ac.ir

Research Article

The Effect of Deferoxamine and Vitamin C Supplementation on Ferritin and CRP Levels in COVID-19 Patients

Faranak Behnaz[1], Seyed Ebrahim Sadeghzadeh Sadat[2], Gholamreza Mohseni[2], Mahshid Ghasemi[2]*

[1]*Department of Anesthesiology, Shohada Tajrish Hospital, Shahid Beheshti University of Medical Sciences, Tehran, Iran.*

[2]*Anesthesiology Research Center, Shahid Beheshti University of Medical Sciences, Tehran, Iran.*

ARTICLE INFO

Article history:
Received 25 June 2023
Revised 16 July 2023
Accepted 29 July 2023

Keywords:
COVID19;
Deferral;
Vitamin C;
Ferritin

ABSTRACT

Background: Today, the COVID19 pandemic is one of the most important health system challenges in the world, which doesn't have specific treatment yet. It includes a wide range of respiratory and non-respiratory signs and symptoms, that lead to hospitalization and intensive care units.

Methods: In this study, 78 patients in two groups of 39 patients were included. The case group included 39 COVID19 patients who had specified sign in CT scans and factors of viral infection, high serum ferritin, increased inflammatory factor in the blood. There were two intervention groups (receiving deferoxamine and vitamin C) and the control group (receiving only official protocol drugs of the country). All patients were admitted to the ICU of Shohada-e-Tajrish Hospital and underwent complete cardiorespiratory monitoring. All changes in Spo2, hemodynamics, serum ferritin and CRP were recorded before the study.

Results: This study presented that improved patient had lower ferritin levels than those who were still ill. In addition, prescribing deferoxamine as an adjunct to vitamin C can prevent cytokine storms that was effective for improving the patients with COVID19.

Conclusion: In conclusion. According to the role of deferoxamine and vitamin C in significantly reducing inflammatory factors of ferritin and CRP, they can be used as an adjunctive therapy in patients with COVID19.

Introduction

Now a day, the COVID-19 pandemic is one of the most important challenges in the world health system, and during more than two years of this pandemic and the conflict of more than one hundred and twenty million people, nearly three million deaths and hundreds of millions of unemployed and billions of dollars economic damages, despite the valuable experience of treating physicians and the management of epidemiologists and policymakers in recent years, no definitive cure has yet been found. The disease includes a wide range of respiratory and non-respiratory signs and symptoms, ranging from asymptomatic to very severe and life-threatening conditions that lead to hospitalization and intensive care units.

The virus can be transmitted through respiratory particles and through direct and indirect contact.

It uses proteins on its surface to identify ACE-2 receptors in host cells and enters the cell cytoplasm and starts replicating.

Viral attack on cells causes damage, proptosis, activation of immune cells, expression of proinflammatory cytokines (cytokine storm). According to the amount of virus and factors such as age and underlying diseases, the symptoms of patients vary, and depending on the type of response, it can lead to acute

The authors declare no conflicts of interest.

*Corresponding author.
E-mail address: mahshid.ghasemi@yahoo.com

respiratory distress syndrome, organ failure, and even death. Most of the time, iinflammation is one of the prominent and main features of Covid-19. The increase of ferritin is seen in a large number of patients and in some studies, worsening of the disease with increased ferritin has been reported.

According to the results of the previous studies and the role of ferritin and iron overload in disease outcome, by controlling and reducing serum iron and ferritin by chelators such as deferoxamine can prevent exacerbation of inflammatory conditions and the number of hospitals stays, morbidity, mortality and reduce treatment costs and improve Outcome.

Due to the COVID-19 pandemic and the presence of mortality due to this virus due to the resulting cytokine storm, it is necessary to use adjuvant drugs to reduce mortality due to these inflammatory substances [1]. Studies have shown that iron-containing enzymes are needed to complete the virus replication process, including COVID-19. There is also a poor prognosis for iron overload due to infection with the virus, and iron restriction as a complementary treatment for viral infections may reduce mortality and morbidity in patients. In previous studies, the use of iron chelators such as deferoxamine has been able to prolong the survival of patients with Acquired Immune Deficiency Syndrome (AIDS) [2]. Regarding the importance of this study, although not much information is available about the regulation of iron in COVID-19 patients, but it can be deduced from the way that the virus works, this treatment can be used to treat patients and minimize the mortality and morbidity of this infection.

The virus targets the epithelial cells of the respiratory tract and causes a wide range of symptoms, from asymptomatic infection to severe lung disease in the final stage that requires mechanical ventilation for ARDS [3].

About 6% of patients with severe pulmonary involvement have acute respiratory distress syndrome and multiple organ failure [4].

Almost a quarter of these patients require respiratory support in the intensive care unit, and it is usually associated with high mortality [5-6].

Factors such as old age, male gender and underlying diseases such as diabetes and heart diseases can worsen the condition of the disease [7].

However even young and completely healthy patients sometimes experience respiratory problems due to Covid-19 [8]. Virus-specific factors and host inflammatory responses have an effective role on disease severity and clinical outcomes [9-10].

In general, two mechanisms have been reported for lung damage leading to ARDS: a) ACE2 acts as a mediator of virus entry into the cell, and in addition, by activating protein S through the imbalance of the renin-angiotensin system, it causes alveolar diffusion damage. b) Some corona proteins cause severe apoptosis in lung cells [11].

According to previous studies, the accumulation of platelets in patients with Covid-19 causes the release of fibrinogen and collagen through the activation of the protein kinase pathway [12].

Ferritin is an iron storage protein. Its serum level reflects normal levels of iron and helps diagnose iron deficiency anemia. Circulating ferritin levels increase during viral infections and can indicate virus replication [13-14].

Elevated ferritin levels due to cytokine storm and Secondary Hemophagocytic LymphoHistiocytosis (sHLH) have also been reported in severe COVID-19 patients [15-16].

Cytokine storm in covid-19 causes the production of inflammatory factors such as IL-6, TNF-α, IL-1β, IL-12 and IFN-γ. also liver cells, Kupffer cells and macrophages cause ferritin secretion [17].

Eventually macrophage activation, hyperferritinemic syndrome and thrombotic storm associated with multiple organ damage. Inducing the expression of several proinflammatory mediators such as Ferritin is the result of excessive inflammation process by binding to T-cell immunoglobulin and mucin filament 2 (TIM-2). Kernan K et al have shown that the ferritin H chain activates macrophages to secrete inflammatory cytokines [18]. Cytokine storms and exaggerated host immune responses (e.g., ferritin) contribute to the progression of ARDS, which, if progressing to respiratory failure, is a leading cause of death [19]. The presence of hyperferritinemia is strongly associated with COVID-19 coagulation. Serum iron and ferritin (a marker of oxidative stress) in the bloodstream can act as markers for damaged cells. Too much iron in the bloodstream causes clot's blood abnormally [20-21]. Platelet and red blood cell function is impaired in the presence of elevated serum ferritin and iron [22]. Hyperferritinemia is also associated with structural changes in platelets and red blood cells.

In a hyperferritinemia study, was related to admission to the intensive care unit and high mortality, regardless of the presence of a tumor or rheumatic disease. Specifically, a ferritin concentration of more than 500 ng / ml predicts 58% mortality [23-24]. As the immune system deteriorates, ferritin levels in patients with sHLH increase significantly compared with levels in patients with defective immune systems [16]. However, increasing evidence supports the use of anachinera (a soluble receptor antagonist in IL-1β and IL-1α) as first-line treatment in patients with sHLH hyperinflammation, IL1β and IL-1α with increased ferritin levels Are found to improve after treatment in patients. Thus, Response to treatment can be monitored by serial ferritin measurement [17, 25].

Extracellular ferritin can also directly contribute to the development of cytokine storm as a proinflammatory

mediator [26]. Iron is both necessary for the body and potentially toxic. It is essential for cellular respiration and oxygen transport and is potentially toxic because of its ability to catalyze the conversion of hydrogen peroxide to free radicals. To prevent such damage, all life forms that use iron attach iron atoms to proteins. In all organisms, ferritin is the most important intracellular iron storage protein. Iron is released from necrotic tissue, then hydroxyl radicals are released from damaged mitochondria, and these reactions cause cell membrane damage and cell death.

According this, we have advocated the idea that as well as clearing pro-inflammatory stimuli, iron-targeting therapies, for example iron chelators, may be helpful in preventing over-inflammation. The use of iron chelators is successfully used in the treatment for frequent blood transfusions, such as patients with major thalassemia, myelodysplastic syndromes, reperfusion injury, hemorrhagic shock, sepsis and SIRS, cancer, multiple trauma, tissue necrosis and a wide range of viral infections [27].

Studies show that despite the effectiveness of iron chelators in various inflammatory conditions, it still has no place as a clinical treatment. Because there is no effective treatment for COVID-19, we investigated the use of iron chelators to prevent or ameliorate cytokine storms and their possible survival in patients with severe COVID-19 infection and hyperferritinemia. In order to iron chelators be effective in severe acute COVID-19 infection, adequate doses should be given as soon as possible. However, it is extremely important to pay close attention to a number of issues before prescribing an iron chelator. Deferoxamine (deferoxamine) is used as an adjunct in the treatment of iron overload and accelerates the excretion of iron from the body. It binds to trivalent iron and prevents it from producing a chemical reaction. It also binds to iron ferritin and homosiderin. It is metabolized by plasma enzymes and excreted in the urine, so it is contraindicated in patients with renal insufficiency. Concomitant use with vitamin C increases the ability of this drug to excrete iron. Vitamin C is a powerful antioxidant that is able to eliminate various types of reactive oxygen and nitrogen. It is the most effective antioxidant in human plasma against lipid peroxidation caused by peroxyl radicals [28].

Ascorbate deficiency is common in people with iron overload and may alter iron distribution.

Animal studies have shown that ascorbate replacement in the presence of deferiprone can significantly improve urinary iron excretion [29]. In this study was to evaluate the adjuvant role of deferoxamine treatment with vitamin C to reduce iron overload due to virus infection.

Methods

After obtaining permission and receiving the code from the ethics committee of Shahid Beheshti University (IR.SBMU.MSP.REC.1399.725), and registering a clinical trial in IRCT.ir with the code IRCT20190121042444N3, all patients with COVID-19 and having evidence of involvement in CT scan that hospitalization in Shohadaye Tajrish Hospital in Iran, was considered as the target group.

Sample size according to the alpha (first error of the study) was 0.05, beta (second error of the study) was 0.2, P1 (with vitamin C deferoxamine supplement) was 0.4 and P2 (without supplement) Desferal vitamin C (0.7), 78 people including two groups of 39 people were included in the study.

Then patients with eligibility such as COVID-19, high serum ferritin and increased inflammatory factor in the blood were included in the study. Any patient who met one of these symptoms such as history of kidney failure, sensitivity to deferoxamine, Contraindications to the use of deferoxamine and pregnancy were excluded from the study.

All patients were given the necessary explanations about the study and informed consent and innocence were obtained and the patients entered the study after signing a consent. Subjects were randomly divided into two intervention groups (receiving deferoxamine and vitamin C). It should be noted that all patients received all national protocol drugs for COVID-19 treatment. Serum ferritin and CRP levels were measured in patients before starting the process. All patients underwent complete cardiorespiratory monitoring in the ICU and all changes in Spo2 and hemodynamics were monitored and recorded.

Intervention group: In addition to treating COVID-19 according to the national protocol (pentazole 40 mg Daily, interferon beta three doses daily, dexamethasone 8 mg BD, ivermectin 0.3 mg / kg Daily, enoxaparin 1 mg / kg SC BD, zinc and vitamin D), Desferal was injected at a dose of 20 to 60 mg based on weight for 8 to 12 hours along with 100 mg of vitamin C ampoules at the time of admission to the corona ward. After 7 days of ferritin CRP tests, it was sent again.

Control group: received only COVID19 treatment according to the national protocol and after 7 days, ferritin and CRP tests were sent again.

All information, including demographic information and other variables, was recorded in checklists designed for this study so that all patients' information was recorded in the same way.

Results

To analyze the descriptive information, central indicators such as mean, median, mod and dispersion indices such as standard deviation and variance were used. Since the total number of samples was more than thirty, t-test was used to compare the mean of variables

between the two groups and Chi-square test was used to compare qualitative variables. In all statistical tests, the value of Pi was considered 0.05 for the significance. For analysis the data used SSPS software version 25.

Following the administration of deferoxamine and vitamin C, significant changes were made in patients, so that the patient's hemodynamics, including patients' blood pressure and heart rate, stabilized, and arterial oxygen saturation increased oxygen demand and respiratory distress decreased. Ferritin and CRP levels decreased. Decreased and a relative improvement was achieved in the general condition of the patients.

In this trial, individuals were randomly divided into intervention and control groups so that no significant difference was observed in the mean age difference between the two groups measured by T-Test. Chi2 test was also used to evaluate the relationship between the sexes in the two groups. The results showed that there was no significant difference between the two groups. The results are shown in Tables 1 and 2, respectively.

In order to investigate the effect of deferoxamine and vitamin C on ferritin and CRP, first each group was compared separately before and after administration (deferoxamine and vitamin C) and then the two groups were compared in the same time period.

The following results were obtained:

In the longitudinal study of ferritin changes in the intervention group after re-measurement, its amount was significantly reduced, but in the longitudinal study of the control group, this reduction was not significant. The calculation is visible in (Table 1).

In a comparative study of the two groups, the amount of ferritin after administration of deferoxamine and vitamin C in the intervention group with the control group was significantly reduced, the results of which can be seen in (Table 2).

In the longitudinal study of CRP changes in the intervention group after re-measurement, its rate was significantly reduced and also in the longitudinal study of the control group, this reduction was significant (probably due to receiving antiviral therapy and improving inflammatory conditions).

In a comparative study of the two groups, in addition to the decrease in CRP levels in both groups compared to the beginning of the study, it was observed that CRP levels after deferoxamine and vitamin C in the intervention group decreased significantly compared to the control group.

Table 1- Evaluation of mean ferritin and CRP in calculation with Dependent test in longitudinal evaluation for both variables

		Paired Differences					P value
		Mean	Std. Deviation	Std. Error Mean	95% Confidence Interval of the Difference		
					Upper	Lower	
Pair 1	Ferritin amount before deferoxamine ng / ml	362	131.13	20.73	403.97	320.09110	0.000
Pair 2	CRP level before deferoxamine mg / Dl	27.78	3.31	0.55	26.66120	28.9	0.000

Table 2- Evaluation of the effect of deferoxamine and vitamin C on ferritin and CRP with Dependent test

		Paired Differences					P value
		Mean	Std. Deviation	Std. Error Mean	95% Confidence Interval of the Difference		
					Upper	Lower	
Pair 1	Ferritin amount after deferoxamine ng / ml	-58.68	1402.91	221.82	389.99	-507.35	0.793
Pair 2	CRP level after deferoxamine mg / Dl	10.77	7.06	1.12	13.03	8.51	0.000

Discussion

COVID-19 with involvement of the respiratory system can lead to ARDS syndrome and multiple organ failure.

In a meta-analysis study conducted by Cheng L et al. in 2019, which included 52 records in 10614 COVID-19 patients were analyzed. Ferritin levels were significantly increased in critically ill patients compared with non-critically ill patients, so that the ferritin levels of the deceased were significantly higher than those of the recovered patients. Ferritin levels are significantly higher in patients with diabetes problems, thrombotic complications and types of cancers. Acute liver disease is associated with a high level of ferritin, and its treatment is supportive and transferring the patient to the intensive care unit [30]. As in our study, it was found that having an underlying disease is highly effective in aggravating the critical condition of individuals. Zhou et al. also showed in 2020 that an increase in ferritin levels is associated with a worsening of COVID-19 [31].

In a study by Bennett TD et al. as well as Carcillo JA et al. in 2011 and 2017, hyperferritinemia was related to admission to the intensive care unit and high mortality. Specifically, a ferritin concentration of more than 500 ng/ml predicts 58% mortality [23-24]. Serial measurements of ferritin not only help to monitor the state of hyperinflammation, but also indicate a therapeutic response [17, 25].

As we demonstrated in the present study, people who recovered had lower ferritin levels than those who remained ill.

A 2006 study by Meyer D et al. on iron chelators as a treatment for iron overload in patients with AIDS and tuberculosis reported a positive effect [32].

In a 2019 study by Y Khodour et al., he examined the role of iron as a metabolizing enzyme in DNA and RNA, and highlighted its importance as a regulator of cellular function [33]. Studies by Romeo AM and Chen L also showed that iron is essential for virus replication [34-35].

In a 2003 study, Xiong S et al shows the role of nuclear factor kappa-B (NF-κB), which increases iron content in Cooper cells following the increase of inflammatory cytokines [36].

Li B et al. Showed that deferoxamine, as an iron-reducing agent approved by the US Food and Drug Administration, was tested to eliminate excess iron [37-39].

In most studies of virus diseases other than COVID-19, the effect of iron on the progression of the disease was strongly seen [40-42].

Liu W et al. in 2020, concluded that iron restriction represents a promising adjunctive strategy in the treatment of virus infections through oral absorption or intravenous injection of iron chelators. For example, iron chelator therapy has been shown to prolong the survival of Acquired Immune Deficiency Syndrome (AIDS) diseases and increase intracellular iron accumulation by increasing iron-releasing ferroportin expression [42-43].

Although knowing about iron regulation in COVID-19 patients are little so far, it can be inferred from other virus infections that iron formulation may be a useful adjunct in the treatment of COVID-19 [43].

Same as our study, which used deferoxamine as an adjunct and an iron chelator to prevent or ameliorate cytokine storms and was effective in healing patients.

According to the results of our study, it can be seen that it has a significant effect on the patients' improvement with COVID-19, which can be extended to all other virus therapies, but due to the limitations of our study, it needs further investigation.

CRP levels were also assessed in this study, which in similar studies, both in virus diseases and in COVID-19, had not yet been studied, and in this regard, the present study examined these cases for the first time.

Conclusion

In conclusion, according to the results of this study, the clear role of deferoxamine and vitamin C in the significant reduction of inflammatory factors ferritin and CRP, which themselves play an important role in disease progression and worsening of patients with COVID-19 virus, shows that desferal and vitamin C are positive effect in the treatment of corona virus disease, so based on this study, deferoxamine with vitamin C can be used as an adjunct therapy in patients with severe corona virus disease.

Due to the limitations of this study, including the limited sample size, it is recommended that the effect of deferoxamine and vitamin C be evaluated in a larger group of patients and that further laboratory criteria be considered in future studies.

Acknowledgment

The authors express their sincere thanks to the staff of Shohada Tajrish Hospital, Shahid Beheshti University of Medical Sciences, Tehran, Iran, for their assistance.

References

[1] Wong C, Lam C, Wu A, Ip W, Lee N, Chan I, et al. Plasma inflammatory cytokines and chemokines in severe acute respiratory syndrome. Clin Exp Immunol. 2004; 136(1):95-103.

[2] Adedeji AO, Lazarus H. Biochemical characterization of Middle East respiratory syndrome coronavirus helicase. Msphere. 2016; 1(5).

[3] Wang D, Hu B, Hu C, Zhu F, Liu X, Zhang J, et al. Clinical characteristics of 138 hospitalized patients with 2019 novel coronavirus–infected pneumonia in Wuhan. China. JAMA. 2020; 323(11):1061-9.

[4] Guan W-j, Ni Z-y, Hu Y, Liang W-h, Ou C-q, He J-x, et al. Clinical characteristics of coronavirus disease 2019 in China. N Engl J Med. 2020; 382(18):1708-20.

[5] Chen N, Zhou M, Dong X, Qu J, Gong F, Han Y, et al. Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study. The lancet. 2020; 395(10223):507-13.

[6] Huang C, Wang Y, Li X, Ren L, Zhao J, Hu Y, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. The lancet. 2020; 395(10223):497-506.

[7] Richardson S, Hirsch JS, Narasimhan M, Crawford JM, McGinn T, Davidson KW, et al. Presenting characteristics, comorbidities, and outcomes among 5700 patients hospitalized with COVID-19 in the New York City area. JAMA. 2020; 323(20):2052-9.

[8] Wu C, Chen X, Cai Y, Zhou X, Xu S, Huang H, et

al. Risk factors associated with acute respiratory distress syndrome and death in patients with coronavirus disease 2019 pneumonia in Wuhan, China. JAMA internal medicine. 2020; 180(7):934-43.

[9] Blanco-Melo D, Nilsson-Payant BE, Liu W-C, Uhl S, Hoagland D, Møller R, et al. Imbalanced host response to SARS-CoV-2 drives development of COVID-19. Cell. 2020; 181(5):1036-45. e9.

[10] Tay MZ, Poh CM, Rénia L, MacAry PA, Ng LF. The trinity of COVID-19: immunity, inflammation and intervention. Nat Rev Immunol. 2020; 20(6):363-74.

[11] Hui DS, Chan PK. Severe acute respiratory syndrome and coronavirus. Infectious Disease Clinics. 2010; 24(3):619-38.

[12] Manne BK, Denorme F, Middleton EA, Portier I, Rowley JW, Stubben C, et al. Platelet gene expression and function in patients with COVID-19. Blood. 2020; 136(11):1317-29.

[13] Li Y, Hu Y, Yu J, Ma T. Retrospective analysis of laboratory testing in 54 patients with severe-or critical-type 2019 novel coronavirus pneumonia. Lab Invest. 2020; 100(6):794-800.

[14] Baraboutis IG, Gargalianos P, Aggelonidou E, Adraktas A. Initial real-life experience from a designated COVID-19 centre in Athens, Greece: a proposed therapeutic algorithm. SN Compr Clin Med. 2020; 2(6):689-93.

[15] Velavan TP, Meyer CG. Mild versus severe COVID-19: laboratory markers. Int J Infect Dis. 2020; 95:304-7.

[16] Giamarellos-Bourboulis EJ, Netea MG, Rovina N, Akinosoglou K, Antoniadou A, Antonakos N, et al. Complex immune dysregulation in COVID-19 patients with severe respiratory failure. Cell Host Microbe. 2020; 27(6):992-1000. e3.

[17] Torti FM, Torti SV. Regulation of ferritin genes and protein. Blood. 2002; 99(10):3505-16.

[18] Kernan KF, Carcillo JA. Hyperferritinemia and inflammation. Int Immunol. 2017; 29(9):401-9.

[19] Kell DB. Iron behaving badly: inappropriate iron chelation as a major contributor to the aetiology of vascular and other progressive inflammatory and degenerative diseases. BMC Med Genomics. 2009; 2(1):1-79.

[20] Pretorius E, Vermeulen N, Bester J, Lipinski B, Kell DB. A novel method for assessing the role of iron and its functional chelation in fibrin fibril formation: the use of scanning electron microscopy. Toxicol Mech Methods. 2013; 23(5):352-9.

[21] Kell DB, Pretorius E. Serum ferritin is an important inflammatory disease marker, as it is mainly a leakage product from damaged cells. Metallomics. 2014; 6(4):748-73.

[22] Lipinski B, Pretorius E, Oberholzer HM, van der Spuy WJ. Interaction of fibrin with red blood cells: the role of iron. Ultrastruct Pathol. 2012; 36(2):79-84.

[23] Bennett TD, Hayward KN, Farris RW, Ringold S, Wallace CA, Brogan TV. Very high serum ferritin levels are associated with increased mortality and critical care in pediatric patients. Pediatr Crit Care Med. 2011; 12(6):e233-e6.

[24] Carcillo JA, Sward K, Halstead ES, Telford R, Jimenez-Bacardi A, Shakoory B, et al. A systemic inflammation mortality risk assessment contingency table for severe sepsis. Pediatr Crit Care Med. 2017; 18(2):143-50.

[25] Mehta P, Cron RQ, Hartwell J, Manson JJ, Tattersall RS. Silencing the cytokine storm: the use of intravenous anakinra in haemophagocytic lymphohistiocytosis or macrophage activation syndrome. Lancet Rheumatol. 2020.

[26] Rosário C, Zandman-Goddard G, Meyron-Holtz EG, D'Cruz DP, Shoenfeld Y. The hyperferritinemic syndrome: macrophage activation syndrome, Still's disease, septic shock and catastrophic antiphospholipid syndrome. BMC Med. 2013; 11(1):1-11.

[27] Su L-J, Zhang J-H, Gomez H, Murugan R, Hong X, Xu D, et al. Reactive oxygen species-induced lipid peroxidation in apoptosis, autophagy, and ferroptosis. Oxid Med Cell Longev. 2019; 2019.

[28] Emara A, El Kelany R, Moustafa K. Comparative study of the protective effect between deferoxamine and deferiprone on chronic iron overload induced cardiotoxicity in rats. Hum Exp Toxicol. 2006; 25(7):375-85.

[29] Sarantos K, Evans P, Garbowski M, Davis B, Porter JB. Vitamin C Deficiency in Patients on Long-Term Deferasirox without Supplementation. American Society of Hematology; 2008.

[30] Cheng L, Li H, Li L, Liu C, Yan S, Chen H, et al. Ferritin in the coronavirus disease 2019 (COVID-19): A systematic review and meta-analysis. J Clin Lab Anal. 2020; 34(10):e23618.

[31] Zhou F, Yu T, Du R, Fan G, Liu Y, Liu Z, et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. The lancet. 2020; 395(10229):1054-62.

[32] Meyer D. Iron chelation as therapy for HIV and Mycobacterium tuberculosis co-infection under conditions of iron overload. Curr Pharm Des. 2006; 12(16):1943-7.

[33] Khodour Y, Kaguni LS, Stiban J. Iron–sulfur clusters in nucleic acid metabolism: Varying roles of ancient cofactors. The Enzymes. 2019; 45:225-56.

[34] Romeo AM, Christen L, Niles EG, Kosman DJ. Intracellular chelation of iron by bipyridyl inhibits DNA virus replication: ribonucleotide reductase maturation as a probe of intracellular iron pools. J Biol Chem. 2001; 276(26):24301-8.

[35] Chen L, Xiong S, She H, Lin SW, Wang J, Tsukamoto H. Iron causes interactions of TAK1, p21ras, and phosphatidylinositol 3-kinase in caveolae to activate IκB kinase in hepatic macrophages. J Biol Chem. 2007; 282(8):5582-8.

[36] Xiong S, She H, Sung CK, Tsukamoto H. Iron-dependent activation of NF-κB in Kupffer cells: a priming mechanism for alcoholic liver disease. Alcohol. 2003; 30(2):107-13.
[37] Li B, Espósito BP, Wang S, Zhang J, Xu M, Zhang S, et al. Desferrioxamine-caffeine shows improved efficacy in chelating iron and depleting cancer stem cells. J Trace Elem Med Biol. 2019; 52:232-8.
[38] Debebe Z, Ammosova T, Breuer D, Lovejoy DB, Kalinowski DS, Karla PK, et al. Iron chelators of the di-2-pyridylketone thiosemicarbazone and 2-benzoylpyridine thiosemicarbazone series inhibit HIV-1 transcription: identification of novel cellular targets—iron, cyclin-dependent kinase (CDK) 2, and CDK9. Mol Pharmacol. 2011; 79(1):185-96.
[39] Kumari N, Iordanskiy S, Kovalskyy D, Breuer D, Niu X, Lin X, et al. Phenyl-1-Pyridin-2yl-ethanone-based iron chelators increase IκB-α expression, modulate CDK2 and CDK9 activities, and inhibit HIV-1 transcription. Antimicrob Agents Chemother. 2014; 58(11):6558-71.
[40] Costagliola DG, Montalembert Md, Lefrère JJ, Briand C, Rebulla P, Baruchel S, et al. Dose of desferrioxamine and evolution of HIV-1 infection in thalassaemic patients. Br J Haematol. 1994; 87(4):849-52.
[41] Drakesmith H, Prentice A. Viral infection and iron metabolism. Nat Rev Microbiol. 2008; 6(7):541-52.
[42] Haider BA, Spiegelman D, Hertzmark E, Sando D, Duggan C, Makubi A, et al. Anemia, iron deficiency, and iron supplementation in relation to mortality among HIV-infected patients receiving highly active antiretroviral therapy in Tanzania. Am J Trop Med Hyg. 2019; 100(6):1512-20.
[43] Liu W, Zhang S, Nekhai S, Liu S. Depriving iron supply to the virus represents a promising adjuvant therapeutic against viral survival. Curr Clin Microbiol Rep. 2020; 7(2):13-9.