Review article

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TODAY'S CHALLENGES - TREATMENT OF ANEMIA IN PATIENTS WITH RENAL FAILURE IN COVID-19 CIRCUMSTANCES

Branka Mitić[1,2], Zorica Dimitrijević[1,2], Radmila Veličković Radovanović[1,2]

A high rate of severe anemia wasobserved in patients with acute kidney injury (AKI) and also in patients on dialysis or chronic kidney disease (CKD) who contracted anew infectious disease caused by SARS-CoV-2. The most severe anemia in COVID-19 occurs in people with severe systemic inflammation, which may occur during illness. Recent studies showed that elevated concentrations of D-dimer are associated with lower hemoglobin and higher serum ferritin. A controversial aspect of therapy in patients with kidney diseases and COVID-19 infection is observed in both populations (with AKI or CKD) about the use of erythropoiesis-stimulating agents (ESA) for the treatment of anemia.

Erythropoiesis stimulating agents represent a revolution in the treatment of anemia in patients with kidney disease. But, he combined interaction of the inflammatory and immune systems with the coagulation system is extremely pronounced in patients with COVID-19 infection. The question is how to treat anemia in patients with COVID-19, whether ESAs are potentially harmful or beneficial, what encourages us to continue the treatment of anemia in patients with COVID-19 usingESA and what are the possibilities to reduce or exceed the risks, as well as whether this therapeutic approach is a new challenge in the treatment of Covid-19 infection.

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Key words: *kidney disease, anemia, Covid-19*

[1]University of Niš, Faculty of Medicine, Niš, Serbia
[2]University Clinical Center Niš, Clinic of Nephrology, Niš, Serbia

Contact: Branka Mitić
48 Dr Zoran Djindjić Blvd., 18000 Niš, Serbia
E-mail: miticdrbranka@gmail.com

Introduction

The SARS-CoV-2 virus has caused an insufficiently known infectious disease in the human population, clinically presented as an acute respiratory disease with pneumonia (but also with involving kidney, heart, digestive tract, blood and nervous system). In most cases, the infection either does not produce any symptoms or causes a mild disease similar to flu, which resolves spontaneously. About 16-20% of cases are classified as "serious" or "critical" (1-3). Recent studies (4-10) indicate transmission of the infectious agent in the period before the onset of any symptoms or asymptomatic cases. The infectious period before the onset of symptoms is not well defined, and according to available data (11-13) lasts on average 2 days before the onset of symptoms. It is suggested that the presence of asymptomatic or infectious patients may be a key epidemiological problem to prevent the spread of COVID-19 in dialysis units.

There is no evidence that COVID-19 infection "damages" the kidneys in those with mild to moderate infection. However, when a serious infection develops and requires hospitalization, kidney abnormalities are noticed in 25-50% of the subjects (proteinuria and erythrocyturia).

A small percentage (less than 15%) develops a decrease in renal filtration function (acute kidney damage).The incidence of acute renal impairment (AKI) with SARS COV-2 is mainly due to acute tubular necrosis (ATN) and rhabdomyolysis.

Studies show that the prevalence of chronic kidney disease among patients infected with Covid-19 is about 0.09%-47.05%. There are no reliable data on the long-term consequences of kidney disease in patients who have survived COVID-19 infection (14-16). However, in patients with acute kidney injury (AKI), as well as in those with pre-existing chronic kidney disease and on dialysis, the presence of a high degree of severe anemia is observed. The most severe degree of anemia is observed in people who develop severe systemic inflammation during the course of the COVID-19 disease, with lower hemoglobin values and high

serum ferritin levels being associated with high concentrations of D-dimer, as confirmed by numerous studies.There is a considerable controversy about the use of erythropoiesis-stimulating agents (ESAs) in the treatment of anemia in patients with either acute kidney injury or chronic kidney disease and COVID-19 infection (17).

The relationship between anemia and inflammation is referred to as chronic disease anemia syndrome or inflammatory anemia. Hepcidin, on the one hand, limits the absorption of iron from the intestine, and on the other hand, the release of iron from the depot in the spleen and the liver, and thus modulates the ferrokinetic response in the presence of inflammation. As a result of limiting the entry of iron into the circulation and tissues, the organism is protected from infection, bearing in mind the fact that most microorganisms significantly use iron as a necessary nutrient. Decreased hemoglobin concentrations, with concomitant increases in serum ferritin levels, are clinical signs of hepcidin induction due to iron trapped in depots, even when there is low circulating iron concentration and low transferrin saturation (18).

The treatment of anemia in patients with COVID-19 and renal insufficiency, as well as what potential effects use of ESA may have, beneficial or harmful, are key issues. The interaction of the inflammatory/immune system with the coagulation process in people with COVID-19 infection was emphasized. The presence of blood clots in the venous and arterial systems of patients is often proven in COVID-19 infection. There is also a danger of more frequent clotting of hemodialysis filters, especially when applying the therapy of continuous replacement of renal function. Pulmonary thromboembolism has also been reported more frequently (19, 20). Experience has shown that for many patients with COVID-19, who are in hospital treatment, it is necessary to use more aggressive protocols for thromboprophylaxis.

There is an intense inflammatory phase in patients with severe COVID-19 infection. Characteristically, the effectiveness of agents for stimulating erythropoiesis is very limited in the inflammatory state (21). It is expected that in the state of inflammation during COVID-19 infection, there will be no adequate response to the use of ESA in patients with anemia, regardless of whether renal disease is present or not. Recent studies announce a new class of stabilizers of factors that cause hypoxia. These are oral preparations that, by their effects, stimulate the production of erythropoietin and increase the availability of iron, which can be considered as potentially more effective than ESA in the treatment of anemia in conditions of intense inflammation (22).

Erythropoiesis stimulating agents represent a revolution in the treatment of anemia in patients with kidney disease. They improve the quality of life and at the same time reduce the need for blood transfusions in this patient population (23).

However, it should be noted that the use of ESA enhances platelet aggregation in hemodialysis patients, which can lead to a prothrombotic condition (24). The side effects of ESA to increase the tendency to thrombosis, with the concomitant prothromboticstatin COVID-19 infections, further increase the unfavorable treatment outcome of these patients (25).

COVID-19 infection is often accompanied by a very low hemoglobin concentration, and, in order to maintain systemic oxygenation, often requires the use of blood transfusions, both in patients without and in those with acute renal injury. The use of erythropoiesis stimulating agents in these individuals is not recommended due to the potentially high risk of side effects, which outweigh the potential benefits.

The production of erythropoietin (EPO) in patients with chronic renal failure and those on dialysis, is significantly reduced, which makes these patients incapable to tolerate the anemic effects of COVID-19 infection. Recommendations for the use of erythropoiesis stimulating agents in these conditions differ. For the patients who are hospitalized due to the severe clinical course of COVID-19 infection, and have already received the appropriate dose of ESA during outpatient dialysis treatment, it is recommended to continue with the same dose to achieve 8 to 9 g/di instead of the recommended 110 to 115 g/dl without COVID-19 infection. It is also recommended that the dose of ESA should not be increased if the target hemoglobin cannot be achieved.

Recent data show that in people with COVID-19 infection, high levels of interleukins (such as IL-1β and IL-6) are accompanied by a more severe clinical course and a higher mortality rate. The results of recent studies suggest that the application of therapies focused on the effects of IL-1β and IL-6 can give promising results (26). In connection with these observations, the immunoregulatory effects of EPO have been shown, which include inhibition of monocytes to produce IL-1β and IL-6 and enable the survival of regulatory T-cells (27). There is also growing evidence of the establishment of global anti-apoptotic effects protection of tissues by the action of erythropoietin, especially in the target organs of COVID-19 (28).

The question is whether this encourages us to continue the treatment of anemia in patients with COVID-19, the use of ESA and what are the possibilities to reduce or exceed the risks, as well as whether this therapeutic approach is a new challenge in the treatment of Covid-19 infection.

Hannelore Ehrenreich, a scientist from the Institute of Experimental Medicine Max Planck investigates the effect of endogenous growth factors over 30 years. "For example, we found that dialysis patients extremely well tolerated Covide-19 - and these patients regularly receive erythropoietin" says Ehrenreich.

The production of endogenous erythropoietin, mostly in the kidney tissue, is stimulated by a reduced concentration of oxygen in the tissues. This cytokine is a signaling molecule for erythrocyte precursors in the bone marrow, and its increased

production enables an adequate supply of oxygen to the brain and muscles. Athletes who take synthetic EPO as a doping agent also use a higher degree of oxygenation that erythropoietin causes. EPO, as a pleotropic hormone, acts not only on erythrocytes but also on many other tissues (29, 30).

The possibility of using EPO as a supportive therapy for severe COVID-19 infection is based on beneficial pleotropic effects on respiratory function, acting on several levels:

1) brainstem and respiratory center,

2) lungs, including protection of overall tissue homeostasis, and

3) n.phrenicus, facilitating respiratory motor control. Erythropoietin, as a proinflammatory cytokine, is responsible for inhibiting the expression of NF-κB in lung tissue, inhibits IL-6 and TNF-alpha and improves the level of the anti-inflammatory cytokine IL-10, thus showing a protective effect on the lung parenchyma. By inhibiting erythrocyte precursor apoptosis, EPO increases red blood cell mass and thus improves tissue oxygenation. In addition, beneficial cytoprotective effects in another various tissues, such as heart muscle, endothelial cells, nervous system, retina, kidney, pancreas, include antiischemic, regenerative and anti-apoptotic effects (31, 32).

Experimental models of EPO effect on liver damage shows reduction of cellular edema (caused by LPS, lipopolysaccharide) in liver lobules, infiltration by lymphocytes and necrosis of hepatocytes (33).

The beneficial effects of erythropoietin in patients with acute renal impairment in sepsis have been accompanied by decreased microvascular damage (34), a reduction in renal inflammation and an improvement in renal tissue oxygenation by a reduction in HIF-1 alpha, iNOS and NF-κB, and an improvement in EPO-R, PeCAM-1, VEGF and VEGFR-2 expression (35).

EPO has cardioprotective effects that are manifested by a decrease in the inflammatory response of the myocardium, it reduces the decrease in the potential of mitochondrial membrane and has antiapoptotic effects on heart muscle cells via the mitochondrial pathway and also alters the expression of NF-κB p65 (a major factor in many inflammatory pathways) (36).

EPO can block the activation of NF-κB and thus affect the modulation of cytokines and its regenerative and anti-apoptotic effects, which can prevent the worsening of the clinical course of the disease COVID-19 (37).

The use of EPO against Covid-19 may reduce severe disease progression.

In a condition where brain damage has occurred during Sars-CoV-2 infection, EPO, acting as a growth factor, can prevent progressive disease and long-term adverse neurological effects, as confirmed by recent studies, EPO improves breathing in case of lack of oxygen

It could protect against neurological symptoms and long-term effects of diseases such as headaches, dizziness, loss of smell and taste and seizures.

The effects of EPO, which lead to a decrease in the levels of IL-6 and modulators of the ferrokinetic response in inflammation, such as hepcidin, result, on the one hand, in an increase in the release of iron from macrophages, and on the other, in an increase in iron absorption in the bone marrow. This reduces the availability of iron as an important nutrient for intracellular organisms, such as Coronavirus, and their enzymatic activities (38, 39).

This possibility of the potential antiviral effect of EPO suggests useful use in human viral infections such as HCV, HIV-1, HBV and CMV, and currently COVID-19 infections.

Conclusion

More clinical studies are needed to answer the question of whether the use of ESA is a reasonable choice in critically ill patients with COVID-19 and what is the optimal dose for the treatment of anemia, with maximum cytoprotective and anti-apoptotic effects and minimal toxicity potential.

The therapeutic approach in patients with kidney disease, especially dialysis patients, requires flexibility in treatment strategy, balancing the potential benefits and harms of ESA therapy, in line with the growing knowledge of the pathophysiology of COVID-19 and its treatment.

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LEČENJE ANEMIJE KOD BOLESNIKA SA BUBREŽNOM INSUFICIJENCIJOM U USLOVIMA PANDEMIJE VIRUSA COVID -19 – IZAZOVI DANAS

Branka Mitić[1,2], Zorica Dimitrijević[1,2], Radmila Veličković Radovanović[1,2]

[1]Univerzitet u Nišu, Medicinski fakultet, Niš, Srbija
[2]Univerzitetski klinički centar Niš, Klinika za nefrologiju, Niš, Srbija

Kontakt: Branka Mitić
Bulevar dr Zorana Đinđića 48, 18000 Niš, Srbija
E-mail: miticdrbranka@gmail.com

Kod bolesnika sa akutnim oštećenjem bubrega (AOB), kao i kod bolesnika na dijalizi ili sa hroničnim bolestima bubrega (HBB), koji su oboleli od nove zarazne bolesti SARS-CoV-2, primećena je visoka stopa teške anemije. Najteža anemija, kada je u pitanju virus COVID-19, javlja se kod osoba sa teškom sistemskom upalom, koja se može razviti tokom bolesti, koju ovaj virus izaziva. Nedavna istraživanja pokazala su to da su povišene koncentracije D-dimera povezane sa nižim hemoglobinom i većim serumskim feritinom. Kontroverzni aspekt terapije kod bolesnika sa bubrežnim oboljenjima i infekcijom izazvanom virusom COVID-19 primećen je u obe populacije (sa AOB ili HBB), a odnose se na primenu agenasa za stimulaciju eritropoeze (ESA) u lečenju anemije. Agensi za stimulaciju eritropoeze predstavljaju revoluciju u lečenju anemije kod bolesnika sa bubrežnim bolestima. Ali, interakcija upalnog/imunološkog sistema sa koagulacijom izuzetno je naglašena kod bolesnika sa infekcijom izazvanom virusom COVID-19. Postavljaju se pitanja kako lečiti anemiju kod bolesnika sa virusom COVID-19, da li su ESA potencijalno štetne ili korisne, šta nas ohrabruje da nastavimo lečenje anemije kod bolesnika sa virusom COVID-19 upotrebom ESA i koje su mogućnosti:smanjiti ili premašiti rizike, kao i to da li je ovaj terapijski pristup novi izazov u lečenju infekcije izazvane virusom COVID-19.

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Ključne reči: *bolesti bubrega, anemija, COVID-19*