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Review Article

A Review of Pleiotropic Potential of Erythropoietin as an Adjunctive Therapy for COVID-19

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ABSTRACT

Coronavirus disease 2019 known as COVID-19 is a new high prevalence severe acute respiratory infectious disease. According to the research and statistical data, only in January 2021, about 10 million cases of COVID-19 and more than two million deaths have been confirmed. The main causing factor of this disease was introduced as the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). In addition to the respiratory system, the disease affects the gastrointestinal tract, central-peripheral nervous system, circulatory system, and kidneys. Therefore, any therapeutic action to reduce COVID-19-related symptoms and complications is essential. In this study, we have conducted a new systematic review of the published literature on the efficacy of erythropoietin (EPO) and recombinant human EPO as a safe stimulant and tissue protector in the treatment of COVID-19. We have briefly described the structure of coronavirus, its pathogenesis, and the structure of EPO and recombinant human EPO. All relevant articles which have published in the Science Direct, as well as PubMed, and Scholar-Google databases were explored. According to the results, EPO is a cytoprotective cytokine induced by hypoxia. The pleiotropic effects of EPO are associated with its erythrocyte-forming, anti-apoptotic, anti-inflammatory activities. It also exerts protective effects on the heart, lungs, kidneys, arteries, and central and peripheral nervous systems. It has been demonstrated that EPO can increase hemoglobin levels, thereby increasing oxygen delivery to the tissues. Therefore, recombinant human EPO therapy can be used for counteracting the adverse effects of COVID-19 including hypoxic myocarditis, acute renal failure, pulmonary edema, and brain or spinal-cord ischemic injuries. Overall, the use of EPO and recombinant human-EPO therapy increases blood coagulation, tumor growth, thromboembolism, and purification of red blood cells, which must be accompanied by anticoagulants such as heparin.

Keywords: Erythropoietin; COVID-19; Hypoxia; Recombinant human erythropoietin; Pleiotropic

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INTRODUCTION

Coronaviruses (CoVs) which are a wide population of viruses, can infect human and some animals. The effects of the detected CoVs indicate that this group of viruses is responsible for the development of infectious diseases in human respiratory system. Middle East respiratory syndrome (MERS), and also severe acute respiratory syndrome (SARS) could be mentioned in this group (1, 2). The new group of CoVs called the SARS-CoV-2 that has been discovered late 2019, is responsible for the recent global coronavirus outbreak (1, 3). This virus was initially detected in Wuhan, China late 2019, however by end of January 2020, 92,262,621 new cases confirmed and about 1,995,000 deaths have been recorded. These statistics indicate the disease's rapid growth and spread (1, 4, 5).

COVID-19 is related to poor lung function, respiratory compromise due to alveolar inflammation and cytokine storm, and fever (3). In other words, this disease affects the lungs and respiratory tract, causing the person to suffer from dry cough, which can sometimes progress into a severe form of pneumonia (1). It has been proposed that the angiotensin-converting enzyme 2 forms an infiltration pathway for SARS-CoV-2 in the epithelium of the airways and alveoli that leads to local cell death (6). The virus uses a subunit protein called S1 for binding to the host cell (7); the results of the virus' function in the body disrupts lung tissue and its function as well as the function of other essential organs, such as the heart, kidneys, arteries, nerves, skin, and the central nervous system (1, 6). The mortality rate of COVID-19 is 8.2% in men and 7.1% in women, which might be related to the presence of some genes on the X chromosome (4). Hypoxia seems to be one of the symptoms of COVID-19. An expected body reaction to hypoxia is increased production of erythropoietin; therefore, the use of EPO in the treatment of COVID-19 has been proposed (6, 8). This glycoprotein hormone/cytokine is primarily produced by a molecular signal known as the hypoxia-inducible factor-2 (HIF2), which increases the count of the red-blood-cells (RBC) produced by the bone marrow by inhibiting the apoptosis of erythrocyte precursors. The main source of EPO is the liver during fetal development and kidneys in the adulthood (3, 5, 8, 9). Studies indicate that EPO expression occurs in various body tissues (10, 11). Erythropoietin therapy in COVID-19 improves respiration, reduces inflammation in effect of cytokine storm, and exerts neuroprotective effects on the brain and peripheral nervous system (10). In addition, with lowering the levels of IL-6 and hepcidin, EPO increases iron release from macrophages iron absorption by the bone marrow. Consequently, the virus's access to iron, which is required for its enzymatic activity, is reduced (3).

It is also effective in reducing respiratory disorders through its anti-apoptotic effects, releasing leukocytes from the bone marrow, and affecting the distribution of iron so that it is not exposed to the coronavirus (3, 12). This article aimed to review the effect of recombinant human EPO on COVID-19 and related hypoxia as well as EPO counteraction with apoptosis.

MATERIALS AND METHODS

The Science Direct, PubMed, and Google Scholar databases were systematically searched for published articles about COVID-19 and its treatment with recombinant human EPO. The World Health Organization was also used to obtain COVID-19 related statistics. In our research, relevant articles, were filtered using the terms "Review published during 2016 to 2021", and older articles were used to obtain some definitions of keywords such as EPO and cardiovascular therapies, induction of EPO hypoxemia in COVID-19, pathogenesis, and structure of COVID-19, etc. In general, the criteria for selecting articles included key information like a definition of the mechanism of injury in COVID-19, hypoxic effects and treatments in COVID-19, and therapeutic effects of the

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EPO. Furthermore, published research papers with high scientific impact based on their citation frequency were included in the study. Articles that had been focused on the psychological aspects of the disease were excluded. More than 100 articles were obtained, and only 96 articles were eligible to be enrolled in the study.

RESULTS

Current Perspective, Structure, and Pathogenesis of SARS-CoV-2

Coronaviruses are a large family of viruses that are very diverse in their phenotypes and genotypes (13). These viruses belong to the family Coronaviridea, the order Nidovirales, and the genus Coronavirus. There are four genera within the subfamily Ortho-Coronaviridea, namely α-CoV, β-CoV, γ-CoV, and δ-CoV (14). Furthermore, studies show that both the α- and β-CoV genera are known to infect mammals, while the δ- and γ-CoVs infect birds. SARS-CoV-2 belongs to the genus β-CoV due to its phylogenetic relationships and genomic structure. The Coronaviridae Study Group (CSG) of the International Committee on Taxonomy of Viruses named this virus SARS-CoV-2 because of the close resemblance between its sequences and the CoVs that are associated with SARS-CoV (13, 14, 15, 16). It is a medium-sized, single-stranded, RNA virus with nucleoprotein within a capsid consisting of protein matrix. The name CoV was chosen because of the crown-like ACE2 receptor on the virus's surface (13, 15).

Coronaviruses include the largest length of genome (26.4 to 31.7 kb) among the known RNA viruses, with GC contents varying from 32% to 43% (13, 15). The SARS-CoV-2 genome (average size 30 kb) is a large portion of the unstructured polyprotein (ORF1a/b), which is broken down into 15 or 16 separate proteins including four structural proteins and five lateral proteins (ORF8, ORF3a, ORF6, ORF7, and ORF9) (14). The four structural proteins include glycoproteins (present on the surface), spike protein (S), membrane protein (M), coating protein (E), and nucleocapsid protein (N); the latter is essential for the assembly and infection of SARS-CoV-2. Surface glycoproteins play a key role in host cell attachment and further division by N-terminal (S1 subunit) and C-terminal (S2 subunit) proteins and membrane-bound spike glycoprotein (13, 14). Understanding the structure and function of spike proteins can help produce monoclonal antibodies and vaccines.

As mentioned earlier, CoVs are RNA viruses that can infect the respiratory, circulatory, gastrointestinal, and central nervous systems in various vertebrates such as bats, birds, penguins, snakes, mice, and humans. According to statistics, SARS-CoV and MERS-CoV are highly contagious and have resulted in death of thousands of people in the last two decades (17, 18). Since late December 2019, a new coronavirus called SARS-CoV-2 has caused a global outbreak of a respiratory disease known as COVID-19 (19, 20, 21, 22). Infection with the virus was first discovered in Wuhan, China; this serious contagious infection spreads throughout China and to other countries (17, 22). According to studies, SARS-CoV-2 is thought to have a common human-animal origin due to the similarity of the RaTG13 sequence to the CoV strains found in bats and pangolins. In the next stage, the virus acquires the ability to spread from human to human. Human-to-human transmission of COVID-19 is possible through respiratory particles or direct contact with patients (13, 18). The most common early symptoms of this disease are fever, dry cough, fatigue, diarrhea, etc. (17, 22). Redness and burning of the eyes and loss of smell have also been reported in some patients with COVID-19 (23). In general, the symptoms of COVID-19 range from mild respiratory tract infection to acute complications such as severe progressive pneumonia, multi-organ failure, which could be fatal, especially in elderly patients, people with respiratory or cardiovascular diseases, and immunocompromised individuals (19, 20, 21, 21). Studies show that acute respiratory distress syndrome (ARDS) in patients with

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COVID-19 leads to decreased blood oxygen levels. Generally, when a person inhales through the nose, air travels down the pharynx, larynx, and trachea into the alveoli, where oxygen is transferred from the inhaled air into the blood and then is transported to all body parts. During ARDS, the capillaries inside the lungs leak more fluid into the lungs than normal conditions, preventing oxygen transport from the lungs to other body organs; consequently, the body organs are weakened or paralyzed (24, 25). The probable reason for CoVs infection in the respiratory tract is the presence of dipeptidyl peptidase 4 and ACE2 in the lower respiratory tract, which are the most important human receptors for MERS-CoV and SARS-CoV (14). Similar to SARS-CoV, SARS-CoV-2 uses the ACE2 receptor to enter human cells, which might be due to the high similarity rate (70%) of the genetic sequences between the two viruses (26, 27). However, the spike protein differs between the two viruses. The spike protein in SARS-CoV-2 has more overlap with the ACE2 receptor, thereby facilitating human-to-human transmission (14, 26, 27). With the entry of alveolar epithelial cells and the rapid proliferation of the virus in those cells, a severe immune response coupled with cytokine hyper-secretion syndrome and lung tissue damage occurs (14). Furthermore, the number of T cells, CD4 receptor, and CD8 T cells are reduced, resulting in immune suppression. The resulting secondary infection causes respiratory dysfunction (28).

Recombinant EPO and its structure

Human EPO (EPO) is a 30.4 kDa glycoprotein hormone composed of 165 amino acids (29, 30). By binding to its receptor on the cell surface, EPO receptor (EPOR), EPO acts as a hematopoietic growth factor and stimulates the proliferation, differentiation, and maturation of erythroid progenitor cells during the process of erythropoiesis (8, 31, 32, 33). It induces hypoxia in the liver, renal interstitial cells, neurons and astrocytes, lungs, spleen, and bone marrow (34, 35) and acts as a cytokine with pleiotropic protective effects. The EPOR is a 52 kDa peptide with a single carbohydrate chain (33, 36) and belongs to the class 1 cytokine receptor superfamily. It consists of a WSXWS motif in the extracellular domain, a single global domain, and a cytoplasmic domain without tyrosine kinase activity; the latter is associated with Janus kinase (JAK) and forms homodimer, heterodimer, and heterotrimer complexes (37, 38). Studies indicate the significance of the presence of EPOR on the surface of erythroid progenitor cells to make red blood cells (39, 40, 41 42). However, EPOR expression is not restricted to erythroid tissue. This receptor is also expressed in non-erythroid cells, including neurons, endothelial cells, bone marrow stromal cells, and skeletal muscle myoblasts (41, 43). Using several signaling pathways, such as JAK2, EPO can exert its protective and anti-apoptotic effects on various cells and tissues in the body, including the lungs, kidneys, heart muscles, the nervous system, retina, pancreas, and endothelial cells (12, 30, 44). Erythropoietin is held adjacent to cytoplasmic JAK2 kinases by binding to its homodimer receptor complex, thereby providing the possibility of JAK transphosphorylation, receptor phosphorylation, and activation of signal transducers and activators of transcription (STAT) and other downstream signaling pathways, including alpha serine/threonine-protein kinase and Extracellular signal-regulated kinases (45, 46, 47, 48).

Recombinant human EPO was first discovered in 1985 using recombinant DNA technology (49). It is a glycoprotein with 165 amino acids arranged inside the molecule in a single chain by two disulfide bonds. Moreover, it has an N-glycosylation site in three specific asparagine amino acids (Asn24, Asn38, Asn83) and an O-glycosylation site in Ser126 (50, 51). Types of recombinant human EPO available today include alpha epoetin (Procrit, Epogen, Epogen, and Eprex), which is the first recombinant human EPO treatment product (52), beta epoetin (NeoRecormon, and Recormon), gamma epoetin (Dynepo), and

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omega epoetin (Epomax) (53). Recombinant human EPO is an erythrocyte-stimulating factor with protective effects on the body (44, 53, 54). It is used to treat chronic inflammatory diseases, infants' prematurity, immune system failure, and chronic renal failure-related anemia also known as end-stage renal disease (30, 50, 53, 55, 56). The common β-receptor (βCR), CD131 (also known as the hemopoietin receptor) (57), is a suggested alternative to EPOR (58, 59). It is expressed in non-hematopoietic tissues, including central and peripheral nerve tissue, heart, kidneys, retina, endothelium, and muscles (60), and shares the WSXWS motif in the extracellular part with the EPO (57). Studies on an in-vitro model of colitis in mice indicated the role of heterocomplexes βCR–EPOR in developing the EPO protective response (54), although there is still no clear understanding of its signaling pathway (60, 61). Some studies have shown that EPO derivatives can enhance its protective effects by binding to alternative EPO receptors such as EPOR/βc heterodimer receptor in non-hematopoietic tissues without stimulation of erythrocyte production (58, 61). These EPO derivatives include asialo-EPO, carbamylated EPO, recombinant helix B peptide, and EV-3, an EPO transcript characterized by deletion of exon 3 (62, 63),

Therapeutic effects of EPO on COVID-19

In general, production of EPO at high altitudes can help adapt to hypoxic conditions, which can provide therapeutic goals for the prevention and treatment of COVID-19 (6, 8, 10, 64). Depending on the severity of the disease as well as other factors such as age, underlying conditions, etc., symptoms of COVID-19 may vary and can include inflammatory endothelial damage, shortness of breath, vasoconstriction and pneumonia, neuro-edema, inflammation of the heart, heart thrombosis, stroke, hemolysis, and potential carotid dysfunction. Increasing EPO levels may have a significant therapeutic effect on most of the above pathological features. Recombinant human EPO may effectively suppress silent hypoxemia and the loss of red blood cells in severe cases of COVID-19 (6, 10, 22, 64, 65, 66, 67, 68). The effects of EPO on various organs of the body are discussed below.

Effects of EPO on inflammation and cytokine storm caused by COVID-19

Pneumonia, lymphopenia, lymphocyte depletion markers, and cytokine storm have been described as indicators of severe COVID-19 (3, 4, 10). In this case, the amount of C-reactive protein (CRP), D-dimer, and pro-inflammatory cytokines is significantly increased, which are involved in tissue damage (69, 70, 71). On the other hand, in these patients, the amount of T cells, CD4+ or CD8+ T cells cells, or natural killer cells as well as B cells, basophils, monocytes, and even eosinophils, are significantly reduced. Subsequently, SARS-CoV-2 infection could potentially induce T-cell apoptosis. Nucleotide-binding _domain_leucine rich (NLR), whisch is a family of host immune-dependent pattern-recognition molecules, is resistant to several pathogen viruses. Several experiments performed with double-stranded RNA (poly-I: C) and single-stranded RNA (ssRNA40) analogs show an NLRP3-mediated serious response can be activated by a 'virus-mimeti' RNA strains. Inflammation of NLRP3 is an essential host action to fight infection through sensitivity to viral RNA, which could otherwise be very destructive. In general, this excessive inflammatory response is a major factor in the developing an ARDS with NLRP3 inflammation. In animal studies, EPO could effectively reduce lung damage caused by viral infection by suppressing NLRP3 inflammation, which depends on the activation of EPOR/JAK2/STAT3 and inhibition of the NF-κB pathway (70, 71). Subsequently, the inflammation is significantly reduced by caspase-1 cleavage, leading to the development and progression of COVID-19.

Suppression of pro-inflammatory cytokines by EPO protects cells against apoptosis and repairs tissue lesions. In addition, EPO-R

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which is expressed on several immune cells, thus enabling EPO to regulate their differentiation and activation, and even function directly. Respiratory burst of phagocytes activates macrophage EPO signaling, which causes severe inflammation. Modulation of the immune system and the fight against inflammation by EPO promises another beneficial effect in severe COVID-19 infection. Therefore, EPO, as an anti-inflammatory, immunosuppressive, and antiviral drug, is beneficial for patients with COVID-19. Moreover, known adverse effects of antiviral medications such as anemia, observed during SARS, may be resolved with EPO (10). Recent observations suggest that SARS-CoV-2 infections may produces even kidney or heart failure due to harmful inflammation (during the cytokine storm) which target vascular beds. Erythropoietin is able to significantly protect inflammation caused tissue damage (6).

Effects of EPO on the treatment of blood disorders caused by COVID-19

Erythropoietin has been shown to stimulate the production of red blood cells in hypoxia by binding to REPO on erythroid progenitor cells (25). Recombinant EPO enables development of therapeutic strategies that stimulate erythropoiesis by erythrocyte stimulating factor (ESA) in diseases where the production of normal erythrocytes is impaired (25, 70). Although iron is essential for the normal functioning of various proteins and enzymes, this element can be toxic in the Fenton reaction by producing reactive oxygen species (ROS). Therefore, its availability, absorption from the intestine, transport in the body, storage, and metabolism must be fully regulated. Most of the iron in the body is used to make hemoglobin and is stored intracellularly through chelation with proteins, such as ferritin. Hepcidin is the main regulator of iron homeostasis, and its serum production is highly expanded during infection and severe inflammatory conditions. Studies show that overexpression of hepcidin occurs through the JAK-STAT3 pathway and pattern recognition receptor signaling in hepatocytes and myeloid leukocytes, reducing iron availability to red blood cells. There is growing evidence that emphasizes the possible role of iron, ROS, and iron-induced damage-associated molecular patterns (DAMPs) in activation of the NLRP3 and NF-κB signaling pathways, respectively. At all stages of SARS-COV-2 infection, the host body must limit the amount of free iron available to pathogens in order to prevent increased infectivity and pathogenicity (56, 68, 70, 71, 72, 73). In general, hepcidin overexpression due to SARS-CoV-2-related infection and inflammation causes iron deposition in mononuclear phagocytes, which leads to the growth of pathogenic agents that are highly sensitive to the amount of iron. In this condition, macrophages begin to express high levels of pro-inflammatory cytokines. Generally, EPO may also affect iron storage by transferring it to bone marrow, reducing available free iron. The role of EPO is to redistribute iron to produce enough hemoglobin (68, 70, 71, 73).

There is some evidence that exogenous EPO administration to healthy volunteers can significantly reduce serum hepcidin without affecting serum iron levels (68). Moreover, EPO effectively inhibits activation of the NF-κB and JAK/STAT3 pathways, which may be induced by DAMP, iron, and iron-induced ROS (68, 70, 71). Experiments show that most COVID-19 patients shows seroious anemia; this probably can be partly due to the changes in hepcidin and irregular iron metabolism. On the other hand, as mentioned in the previous sections, patients infected with SARS-CoV-2 usually have a severe inflammatory response. Studies show that in conditions like inflammation, erythrocyte production stimulants have very limited effects on red blood cell production; therefore, in patients with healthy or compromised kidneys where anemia due to inflammation is unlikely, an effective response to erythrocyte production is impossible. However, it can be hypothesized that in patients with COVID-19, there may be a link between the elevated

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cytokinin and the concomitant effects of hepcidin levels and irregular iron metabolism. Effective agents in stabilizing hypoxia-causing factors are oral drugs that increase EPO production and increase iron availability. Preliminary results indicate that these drugs can treat anemia more effectively in the inflammatory environment than erythrocyte production (70, 73).

Effects of EPO in the treatment of COVID-19-related cardiovascular disorders

Many studies in the United States, China, and Italy indicate that the new CoV also attacks the heart. To prove the link between heart diseases and COVID-19, researchers have pointed out the followings:

- High mortality rates among patients with the new CoV have a history of cardiovascular disease and hypertension.
- Elevated blood troponin level is a biomarker of cardiomyocyte damage and has been observed in patients with acute disease.
- Infection of the heart muscle in patients with no history of the disease.

The new CoV has many similarities to the pathogens MERS and SARS in terms of cardiovascular symptoms (2). The SARS-CoV-2 infection can develop several cardiovascular abnormalities, including bou not limited to cardiomyopathy, myocardial injury and myocarditis or even pericarditis. Other abnormalities like and cardiac arrest following arrhythmia, heart failure, and coagulation abnormalities are reported too. Many patients have suffered from cardiac symptoms like palpitations, chest stiffness, or acute cardiovascular injury (65). Patients with cardiovascular diseases and hypertension have a higher risk of developing severe COVID-19. Myocardial damage, which may diagnosed by high levels of cardiac disease biomarkers, is due to ischemic and/or non-ischemic reason such as myocarditis (74, 75, 76 77). Numerous studies suggest an acute myocardial injury in patients with COVID-19 (65, 77). Limited cases of COVID-19 analysis indicate a significant interstitial influence on pro-inflammatory mononuclear cells in cardiac tissue, which confirms the myocardial injuries (78, 79). Recently, Tavazzi have reported the first case of SARS-CoV-2 pathogens in the heart. They reported that the heart could be directly infected with SARS-CoV-2 (77). Hu et al. also reported a 53-year-old patient with COVID-19 admitted to the intensive care unit due to systolic dysfunction and viral myocarditis (65).

Furthermore, cardiac arrest leading to sudden death is frequently seen in COVID-19 (74, 80). Among 85 cases of death due to COVID-19, the leading cause of death with seven cases was the cardiac causes (81). Chances of survival of COVID-19 patients with acute symptoms of cardiac arrest are relatively poor (82). Despite all the available interpretations, there is still no credible and direct evidence to confirm cardiac arrest as a complication of COVID-19 (83). However, EPO has beneficial, anti-ischemic, regeneration-promoting, and anti-apoptotic effects on a variety of tissues, including the lung, kidney, heart muscle, nervous system, retina, pancreas, and endothelial cells (12, 44), which are exerted through its specific receptor EPOR/βCR (84).

Furthermore, EPO stabilizes vascular integrity, increases the number of endothelial cells, and protects these cells against ischemia and apoptosis. Due to its molecular mechanism of action of EPO, it induces Ca 2+ in the EC aorta by activating the phospholipase C-γ1 (PLC-γ1) signaling pathway, which leads to the activation of a potential transient receptor vanilloid 1 (5). After the autopsy of patients with COVID-19, researchers in Switzerland found that in some patients, the whole-cell layer is inflamed in the inner layer of blood vessels and lymph of various organs. The researchers concluded that the CoV, through ACE-2, causes inflammation in the intravascular layer. This inflammation can lead to minor circulatory disorders, which damage the heart and can lead to pulmonary

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embolism and blockage of arteries in the brain and gastrointestinal tract (66). Moreover, EPO treatment in rats show that they protect the heart by reducing the myocardial inflammatory responses and mitochondrial membrane potential and reducing myocardial cell apoptosis through the mitochondrial pathway by reducing NF-Kb p65 expression (24).

Therapeutic effects of EPO on pulmonary arteries

Studies show that most COVID-19 patients suffer from acute lung damage. Due to the prevalence of vascular damage in the different tissues, the main roles of EPO is to protect the pulmonary endothelium and prevent pulmonary edema. Experiments on mice show that EPO plays an important role in suppressing pulmonary edema and reducing the swelling of alveolar epithelial cells in acute pulmonary damage due to ischemia-reperfusion injury. Another study by Heitrich et al. on mouse models of acute sepsis-induced lung injury and acute kidney injury showed that EPO, through the expression of EPO-R and vascular endothelial growth factor/ vascular endothelial growth factor 2, had protective effects on the lungs and kidneys (79). This may be related to improved oxygen supply for tissues, which will lead to the reduction of inflammation stimuli (10, 66). Moreover, the anti-inflammatory effects of erythropoietin in protection of lung damage have been reported in animal models too. The critical mechanism for this level of the pulmonary edema is vasoconstriction due to hypoxia in the pulmonary arteries and capillaries. Redistribution of blood flow from the basal regions to the apical surface of the lungs also is effective. In this case, EPO counteracts the constriction of the pulmonary arteries by increasing the endothelial capacity to produce nitric oxide (NO), which causes vasodilation. Studies in transgenic (Tg6) mice injected with large amounts of human EPO revealed that despite the upper hematocrit level of 80% roughly, the blood pressure, heart rate, and output were in the normal range, which may be due to step by step cardiovascular adaptation by consequently NO-induced vasodilation (10). Compatible mechanisms with erythrocytosis in animals also include extra-activity of endothelial NO synthase molecules (eNOS). Moreover, increased NO synthesis by eNOS in Tg6 mice induced dilation of the peripheral arteries. When this experiment was replicated on Tibetans and Andeans, the increase in NO metabolism in lungs of these people acted as an alternate mechanism that counteracts the lack of oxygen at high altitudes. In conclusion, EPO can be an effective selection in therapeutic strategy to prevent acute lung injury and edema caused by SARS-CoV-2 by protecting the pulmonary vascular endothelium and causing vasoconstriction (10).

The effects of EPO in the treatment of neurological disorders caused by COVID-19

Studies have shown that coronaviruses can attack the central nervous system and induce neurological diseases (10). Moreover, studies on the neuro-therapeutic potential of EPO after ischemic injury of the central nervous system in patients with COVID-19 produced acceptable results. Due to improved tissue oxygenation, EPO can act as a neuroprotective, anti-apoptotic, antioxidant, angiogenetic, and nootropic agent. In 2005, Brines and Cerami showed that EPO receptor cells in the central nervous system (astrocytes, neurons, oligodendrocytes, and nerve progenitor cells) could act as a line of defense against damage caused by ischemic events and prevent apoptosis (50). On the other hand, aging is one of the most important factors in cerebral ischemia. Studies show that older mice with ischemic stroke have significant differences in neuroinflammation, increased permeability of the blood-brain barrier, high rate of severe apoptosis, myocardial infarction, expression of genes associated with reduced cell apoptosis, regulation of inflammatory mediators, and central nervous system dysfunction compared with young and healthy mice. These factors can

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indirectly affect the rate of EPO secretion and its positive effects in patients with COVID-19 (65, 85, 86).

Effects of EPO on COVID-19-induced hypoxia induction

As mentioned in the previous sections, if the body is experiencing a reduction in red blood cells and a lack of oxygen, EPO produced under hypoxic conditions in COVID-19 can compensate for the erythrocyte deficiency by stimulating erythropoiesis (87, 88). Moreover, the kidneys are the main source of EPO production, targeting red blood cell progenitors in the bone marrow which can stimulate the blood cells propagations (9, 87, 88). Therefore, EPO treatment for SARS-COV-2 may help to save hemoglobin levels and consequently improve oxygen delivery to tissues. Lechuga et al. suggested that SARS-COV-2 itself attacks the hemoglobin beta chains, but the EPO can effectively treat red cell deficiency in patients with COVID-19 during hypoxemia (87). In addition, EPO could be a good treatment option for short-term medical emergencies of silent hypoxemia. It has been reported that EPO can exert neuroprotective effects in ischemic stroke and brain injury and prevents cardiorespiratory dysfunction that occurs following intermittent hypoxemia (6). Thus, EPO can reduce the severe neurological symptoms caused by COVID-19 by acting on both the central and peripheral systems. According to Khoo et al., SARS-CoV-2 may specifically affect brainstem function, which can be neutralized with EPO therapy (89). In conclusion, increasing the level of EPO is one of the most promising ways to deal with the adverse effects of hypoxemia in COVID-19 (6).

EPO restriction

The amount of D-dimer in patients with COVID-19 increases significantly, followed by many distinct blood disorders caused by the deposition of coagulation fibrin filaments in small blood vessels, lymphatic capillaries, accompanied with the deposition of these fibers outside the cell (67). Moreover, studies show that patients with severe COVID-19 often have prolonged prothrombin, increased D-dimer levels, and decreased fibrinogen and disseminated intravascular coagulation (67, 73). Inflammatory cytokine storm is a hallmark of COVID-19. In patients with severe infections, shortness of breath and lymphopenia are accompanied with elevated levels of IL-2R, IL-6, IL-10, and TNF-α. The severe secondary inflammatory condition leads to a reduction in homeostasis and a marked change in coagulation parameters. The deterioration of coagulation parameters during COVID-19 could lead to various life-threatening complications (90).

Despite its numerous benefits, EPO can aggravate blood coagulation disorders and deterioration of various organs by forming microthrombosis (91). Other side effects of recombinant human EPO administration include high blood pressure, increased tumor growth, thromboembolism, anaplasia of pure red blood cells, etc. (67, 73). Experimental results also indicated arterial hypertension as another side effect of recombinant human EPO, which increases the risk of cardiovascular disease (67, 68, 70), resulting in vasoconstriction (90) as well as dysregulation of the renin-aldosterone system (reduced excretion of sodium by the kidneys) (25, 71). However, the hypertensive effects of recombinant human EPO are independent of its erythropoietic activity (68, 70). In addition, current reported research claim that infection with SARS-CoV-2 is likely to predispose its victims to thrombosis (92).

DISCUSSION

Erythropoietin is a hematopoietic factor that stimulates erythrocyte production. The gene encoding EPO is located on chromosome 7 and encodes a polypeptide that consists of four α-strands (8, 31, 68). As the atmospheric oxygen pressure decreases at high altitudes and certain tissues in the body may become hypoxic, the need to produce erythrocytes to carry more oxygen

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to the tissues increases. This results in increased expression of EPO. On the other hand, the expression of EPO stimulates erythroid progenitor cells in the bone marrow to increase erythrocyte production (10, 34, 35, 93, 94). The receptors of EPO are expressed on erythroid cells, nerve cells, stromal cells of bone marrow, lung, liver, heart, and brain cells (68, 95, 96). In addition to producing erythrocytes and reducing the possible risks of hypoxia, EPO has anti-apoptotic properties that have been observed in kidney cells, lungs, etc. (30, 44). Further research led to the production of recombinant human EPO, which is made by recombinant DNA technology (49, 53). One of the functions of recombinant human EPO is to stimulate the production of erythrocytes in the body (44, 53, 54). The results indicate that EPO derivatives, which bind to a specific receptor, have protective effects on non-hematopoietic tissues independent of erythrocyte production (62, 65). In acute hypoxemia of nerve tissue following COVID-19 in the central nervous system, EPO prevents nerve cell apoptosis (65). According to Sahebnasagh et al., EPO effectively reduces COVID-19-related lung damage by suppressing NLRP3 inflammation (68), which acts as a host defense mechanism against viral RNA infection by suppressing pro-inflammatory cytokines (6, 10). Furthermore, EPO increases iron storage and transports iron to the bone marrow, decreasing hepcidin, the main regulator of iron homeostasis (68, 70, 71, 73). The presence of EPOR-βCR on the lungs, kidneys, and endothelial muscles, with anti-ischemic, regenerative and anti-apoptotic effects, stabilizes vascular integrity and protects against ischemia and apoptosis (5, 44, 84, 96). In some patients with COVID-19, the entire intracellular layer of blood and lymphatic vessels of various organs become inflamed, which is caused by ACE2 that disrupts blood flow and causes heart damage. This can eventually lead to pulmonary embolism and blockage of arteries in the brain and gastrointestinal tract. Erythropoetin reduces the myocardial inflammatory response and mitochondrial membrane potential by protecting the heart and reducing myocardial cell apoptosis through the mitochondrial pathway by decreasing the NFKB p65 expression (5, 44, 84). Studies show that injection of human EPO into mice increases NO metabolism by stimulating the activity of eNO, an adaptive mechanism that protects the pulmonary vascular endothelium and prevents vascular adaptation (10). In general, EPO therapy has numerous benefits COVID-19, but the limitations such as risk of microthrombosis and blood failure in some organs should be taken into account (91). Recombinant human EPO increases arterial blood pressure and causes cardiovascular disease, directly affecting vasoconstriction and disrupting the renin-aldosterone system (25, 67, 68, 70, 71, 90). In conclusion, to prevent coagulation and anemia in patients with COVID-19 by EPO, it is advised to co-administer anticoagulants or antithrombotic agents, such as heparin (6).

CONCLUSION

Erythropoietin can act as a neuroprotective, anti-apoptotic, antioxidant, angiogenic, and erythrocyte precursor stimulant against hypoxia-induced damages. The function of EPO and recombinant human EPO can reduce or eliminate the adverse effects of COVID-19. However, EPO should be used with caution for treatment of COVID-19. A real gap in the current knowledge of applying EPO for treatment of COVID-19 patients is the dosage regarding the increased velocity and risk of thrombosis. Logically, this dosage gap needs more animal research to be determined. However, based on our experience, some of the animal experiments on SARS-CoV-2 may not extend to human cases. Therefore, prescribing lower and safe doses in critical patients may be a promising approach.

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Conflict of interest

The authors declare that there is no conflict of interest regarding the publication of this article.

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