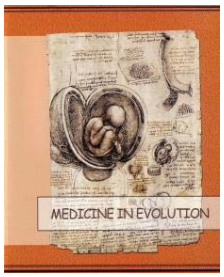
Decreasing the risk of complications in Covid-19 patients by prescribing substitute erythropoietin



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Abstract

Substitutes of erythropoietin (Epo) prescribed to the Covid-19 confirmed patients might increase blood oxygenation. A higher benefit will be in comorbidities patients because Epo may lower complications such as acute respiratory distress syndrome, myocardial dysfunction, and acute kidney injury. Exogenous erythropoietin downregulates inflammatory T cells and myeloid cells responses and reduces endothelial activation. Multiple myeloma patients treated with recombinant human erythropoietin (rHuEpo) for anemia have a prolonged survival rate. In inflammatory response, Epo level drops, hepcidin level increases and affects the iron metabolism by blocking iron inside macrophages. A low dose of rHuEpo administered three times a week is enough for healthy moderate athletes to maintain an increased hematocrit and maximum oxygen volume approximately 5% –10% above the initial levels. Under these circumstances adding rHuEpo may improve the blood oxygenation level from 5% to 20%, which is a great contribution in tissular oxygen levels and enhance humoral immunity.

Keywords: erythropoietin, organ protection, lower complications, Covid-19

INTRODUCTION

Erythropoietin (Epo) is the hormone responsible for the production and regulation of red blood cells [1]. Epo is produced especially in the kidney, but in many other tissues. And also it has been synthesized as recombinant human erythropoietin (rHuEpo) to treat different conditions. These are anemia caused by hematologic disorders or induced by renal failure and lately there were conducted different studies that prove its effectiveness in organ protection, including brain and heart [2]. The recent study rewarded at Nobel 2019 has discovered how cells sense and adapt to oxygen availability[3]. Our understanding of how oxygen levels affect cellular metabolism and physiological function increased, leading the way for new ways to fight anaemia, cancer and other diseases, including Covid-19 [2].

Aim and objectives

This article aims to show the importance of Epo as adjuvant to the Covid-19 treatment and prevention of its severe and critical forms, by increasing blood oxygenation, humoral immunity, and organ protection. This may lead to a lower rate of complications in most of the patients, also in individuals with comorbidities such as diabetes or heart diseases.

MATERIAL AND METHODS

1. Epidemiology and clinical features of critically ill Covid-19 patients

Most severe and critically ill patients are over 50 years old, and about 30% to 50% of Covid-19 patients have chronic comorbidities. At about 7 days (5-12 days) from the initial symptoms a "cytokine storm" and respiratory failure may appear. Also patients may develop hypoxemia without signs of respiratory distress. These patients could associate also, other organ dysfunction [2].

The number of persons infected with Sars-CoV exceeded fourteen million Covid-19 cases worldwide on July 18, 2020; the case fatality rate across 210 countries and territories was 5·2% [4]. WHO-China Joint Mission of 55 924 laboratory-confirmed cases in China were appreciated severe in 13.8% cases (dyspnoea, respiratory rate ≥30 breaths per min, oxygen saturation ≤93%, the partial pressure of arterial oxygen to fraction of inspired oxygen ratio 50% within 24–48 h) and 6.1% were classified as critical (respiratory failure, shock, and multiple organ dysfunction or failure)[5].

The Covid-19 critically ill patients, mainly elderly, with more comorbidities such as hypertension and diabetes, carry a higher risk than non-critically ill patients [2]. Fever, cough, fatigue, and dyspnoea are some of the nonspecific symptoms [6,2]. The time from the first symptoms to the development of pneumonia is approximately 5 days [2,6] and the medium time from symptom burst to severe hypoxemia and intensive care unit (ICU) admission is around 5–12 days [6]. Most of the patients have pathognomonic bilateral opacities on thoracic CT and chest radiography [6].

The most common complication in 60%–70% of patients admitted to the ICU is acute hypoxaemic respiratory failure sometimes complicated with severe hypercapnia, with acute respiratory distress syndrome (ARDS), followed by shock (in 30% cases), myocardial dysfunction (20%–30%), arrhythmia (44%), and acute kidney injury (10%–30%) [2,6]. Although, elderly patients might develop hypoxemia without respiratory distress.

2. Inflammatory response and Epo activity

Epo and cytokines

Erythropoiesis is controlled by different regulators, such as Interleukin 3, granulocyte-macrophage colony-stimulating factor, and also stem cell factors that play regulatory functions in the early stages of erythropoiesis. Erythropoietin is the main positive acting factor in the last steps of erythrocyte production in mammals. Epo is specific for erythroid

progenitor cells and has only a small effect on other cells. The target cells for Epo are the progenitors of erythroid (BFUe and CFUe), therefore Epo acts on these via Epo-specific surface receptors. Epo induces proliferation and differentiation of erythroid progenitors eventually leading to reticulocytes. During this process, certain conditions are required to allow this differentiation: progenitors must be enough, the bone marrow environment must be normal, and nutrients such as folic acid, vitamin B12, and especially iron must be available.

Elementary iron is an absolute necessity for adequate hemoglobin formation. In a normal adult, without any stimulation, the bone marrow synthesizes 4×10^{14} hemoglobin molecules per second, each molecule containing four iron atoms, which corresponds approximately to 20 mg iron [2]. Conversely, erythropoiesis is negatively regulated by several cytokines. These are cytokines derived from macrophages, inclusive tumor necrosis factor (TNF-α), interleukin-1 (IL-1), interleukin-6 (IL-6), and growth transformation factor-β (TGF-β). All these factors are enhanced in inflammatory conditions and are involved in the pathogenesis of chronic anemia. TNF-α has an inhibitory effect on erythroid progenitors either directly or mediated by interferon-β (INF-β). IL-1 inhibits erythropoiesis in vivo in mice and in vitro in humans. Also, inhibition is direct or mediated by INF-β. TGF-β induces anemia when injected into mice and inhibits colony formation by erythroid progenitors. IL-6 injected in vivo induces anemia, but the inhibitory effect on erythropoiesis in vitro is unclear. These cytokines affect the metabolism of iron by blocking iron inside macrophages [5]. Inflammatory cytokines induce iron metabolism. In all types of infectious or inflammatory disorders a significant hypoferremia is observed despite adequate iron deposits. Probably this is a consequence of the unparalleled release of iron from the monocyte-macrophage system. The iron is not available because of its sequestration in the monocyte-macrophage system. Activated macrophages and granulocytes synthesize lactoferrin, a protein which is competing with transferrin for iron-binding [2]. More IL-1 has been reported to increase ferritin production, and this extra ferritin could act as an iron trap that might otherwise be available for erythropoiesis. Impairment of iron metabolism certainly contributes to erythropoiesis affected in inflammation, but it is not its most important contribution [2]. Experimental animal studies have confirmed the relationship between inhibition of erythropoiesis and inflammatory cytokines. Chronic TNF-a injection in animals produces a high development of anemia [2]. This effect is specific to erythroid because neither granulocytes nor platelets are affected. Similarly, infections of TGF-β in mice induce a severe and progressive manifestation of manifested erythropoiesis by a decrease in the reticulocytes number and spinal cord erythroblasts. The effect seems to be indirect and mediated by TNF.

Epo and organ protection

A surprising finding in neural protection research on Epo was that carbamylated Epo, which does not bind to the canonical Epo receptors (EpoR) and transduce the signaling cascade mediated by JAK2-STAT5 also showed neuroprotective effects [7]. Carbamylated Epo also has the cardioprotective effect of Epo. Asialoerythropoietin failed to increase erythropoiesis, but conferred protection of neurons in vivo [7]. The pleiotropic effect of Epo is mediated by non-canonical heteromultimeric composed of EpoR and common β subunit, the common granulocyte-macrophage subunit colony-stimulating factor, IL-3 and IL-5 receptors in injuries of spinal cord. It should be noted, however, that β subunit is not always necessary to transduce Epo signals to protect against apoptosis [7]. Subsequent characterization of the structure of the mediating cellular receptor pleiotropic effects of Epo in non-hematopoietic cells are required.

The protection of organs by non-erythropoietic Epo derivatives led the investigators to delimit the areas of protection of tissues from Epo to amino acids that form the aqueous face of the B helix [8]. Pyroglutamate the helix B surface peptide was effective in ameliorating multiples organ failure in a pattern of hemorrhagic shock [7].

New mechanisms elucidated of tissue protection through Epo. Hu et al. proves that Klotho is protective; the effect against oxidant-induced cytotoxicity is partially mediated by one year increasing the endogenous expression of the classical EpoR [9]. While erythropoiesis is stimulated by canonical EpoR homodimer, the Epo protective effects on tissues are mediated by a "tissue-protective" heterodimeric receptor [9].

RESULTS

1. Epo activities in several diseases

Epo and malaria

During the sanguine stage of malaria a reduction of circulating hemoglobin should be noticed. Also, tissue hypoxia should elevate the levels of Epo, but the clinical evidence for appropriately raised levels of Epo is contradictory.

Studies from Thailand and Sudan have suggested that Epo concentrations, even if raised, were still very low for the degree of anemia [10]. An experimental research in murine malaria suggests that exogenous Epo can improve the integrity of the blood-brain barrier, downregulate T cells and myeloid cells inflammatory responses and reduce endothelial activation [10].

Anemia in chronic diseases and inflammatory response

rHuEpo is available for the anemia treatment secondary to renal failure [11], and also other causes such as solid and hematological neoplasms. Besides its erythropoietic action, Epo has been shown to have pleiotropic effects [11]. These results were supported by the demonstration of Epo receptors on non-hematopoietic tissues and different cells. It has been previously observed that patients with multiple myeloma (MM) treated for anemia have demonstrated a prolonged survival rate [12]. Using a mouse model, it has been demonstrated that Epo has a mediated anti-myeloma effect. Additional studies have shown that many of the cellular immune deficiencies commonly encountered in MM and myelodysplastic syndromes patients are corrected in patients treated with rHuEpo for anemia [13].

Hepcidin is the primary regulator of iron availability to developing C- reactive protein (CRP) and is increased in chronic inflammatory conditions including anemia of chronic disease /anemia of inflammation (ACD/AI). If the hepcidin levels increase, the iron will remain blocked in the cells thus it will lead to anemia. The anemia of chronic illnesses was initially associated primarily with infectious, inflammatory, or neoplastic disease, but it has been shown that conditions including obesity, diabetes mellitus, congestive heart failure, severe trauma, and other forms of acute or chronic immune activation produce ACD [14]. Administration of Epo or other darbepoetin (erythropoiesis-stimulating agent) may have an antiinflammatory effect and reduce hepcidin expressions. Both agents have been used for the treatment of ACD/AI for many years.

Patients with inflammatory conditions treated with antitumor necrosis factor TNF (antibody) or anti-IL-6 antibody show reductions of inflammatory markers, such as IL-6, hepcidin, and/or CRP, which correlate with the improvement of anemia. The measurement of Epo concentration is indicated for ACD/AI patients who show symptomatic anemia and / or anemia that does not improve after the treatment of the main disorder with or without iron supplements. In these casehats, it suggests a low level of Epo is due to a continuous inflammatory block or perhaps a more serious kidney disease than previously considered.

A very high Epo level suggests insufficient erythropoiesis due to bone marrow disease, such as myelodysplastic syndrome.

The elevated levels of IL-6 and TNF-α are imposing a higher dose for darbepoetin in patients with kidney disease.

Recent evidence suggests that vitamin D can suppress hepcidin (14). Anemia and vitamin D deficiency sometimes coexist and enhancement of vitamin D deficiency can

improve anemia in a certain percentage of people; this is believed to function by direct inhibiting of hepcidin formation by the active vitamin D [15,14].

2. Prophylactic effects of Epo (erythropoietin enhances oxygenation)

A multicentric study demonstrated that erythropoietin enhances oxygenation [16]. It proved that in critical ischemic and hypoxic surrounding tissue, using Epo as pretreatment improves tissue infusion and oxygenation in vivo. This effect can be attributed to Nitric Oxide (NO)-dependent vasodilatory and anti-inflammatory actions on the altered vascular endothelium. We thought about the effect of recombinant human erythropoietin on the microcirculation and oxygenation of critical ischemic tissue and how to elucidate the role of nitric oxide endothelial synthase in the protection of erythropoietin mediate tissue. A critically ischemic hypoxic area and some other island flaps were dissected from the back skin of an anesthetized Syrian male golden hamster which has been infused through a collateralized vasculature. Before ischemia, animals received a shot of epoetin beta at a dose of 5,000 U / kg body weight with (n = 7) or without (n = 7) NO block synthase with 30 mg/kg body weight L-NUME (methyl ester hydrochloride N5-nitro-L-arginine). Animals treated with saline as a control group (n = 7). After 5 hours of collateralization, ischemic tissue damage was characterized by severe hypoperfusion and inflammation, hypoxia, and accumulation of apoptotic cell nuclei. Pre-treatment of erythropoietin increased arteriolar and venous blood flow by 33% and 37%, respectively ($P<0.05$) and attenuated leukocytic inflammation around 75% ($P<0.05$). In addition, the partial pressure of oxygen in the ischemic tissue increased from 8.2 to 15.8 mmHg ($P<0.05$), which was in parallel with a 21% increased density of patent capillaries ($P<0.05$) and a 50% reduced number of apoptotic cells ($P <0.05$). Improved microcirculation and oxygenation were associated with a 2.2-fold ($P<0.05$) increase in endothelial NO synthase protein expression. Interestingly, N5-nitro-L-arginine methyl ester hydrochloride totally eliminated all the beneficial effects of Epo as pretreatment [16]. It has been proven that both Epo mRNA and proteins are found in the brains of a variety of mammals, including humans. The Epo receptor is widely expressed in most types of brain cells, including neurons, endothelial cells, microglial cells, and astrocytes. **Table 1** provides an overview of the cellular sites of Epo and EpoR expression in the central nervous system [17].

Table 1. Sites of Epo and EpoR expression in the central nervous system in humans, modified after[17]

	Epo		Epo receptors	
Cell types	In vitro	In vivo	In vitro	In vivo
Neurones	-	+	+	+
Astrocytes	+	+	+	+
Microglial cells	-	NA	+	NA
Endothelial cells	NA	?	+	+

+, expression detected, NA Not analyzed, ? not proven

A clinical evidence is stated in a recent study that analyzed the improvement of Epo treatment for neonates with moderate to severe hypoxic-ischemic encephalopathy. Epo reduces the risk of MRI brain injury, cerebral palsy, and moderate to severe cognitive impairment [18]. The evidence is limited to suggesting its role as an adjunct to hypothermia. Higher power studies are underway to overcome this limitation [18]. The usage of Epo substitutes athletes to improves their performance by enhanced oxygen level.There has been confirmed that a low dose of rHuEPO (20 IU/ kg body weight) administered three times a week is enough for healthy moderate athletes to maintain an increased Hct and maximum oxygen volume (approx 5% –10% above the initial levels), which can be achieved in itself within 3-4 weeks of a more aggressive dose (50 IU/kg body weight, three times a week). During submaximal exercise with intensities of up to 81% of baseline maximum oxygen volume was generally lower thereafter administration of r-HuEpo [19].

3. **Humoral immunity improvement in vaccination associated with rHuEPO treatment**

Humoral immunity can also be enhanced by rHuEpo treatment. A benefic effect on cell-mediated immunity and humoral immunity (hepatitis B vaccine) was produced by RhuEpo treatment, and also in response to the seasonal flu vaccine. In a study on hematologic patients, three groups of individuals received the flu vaccine [20]. These were divided as follows: healthy controls, hematological patients with no rHuEpo (NoEpo group), and rHuEpo treated hematological patients for their anemia (Epo group). The anti-influenza Ab titer was measured (complement fixation test) from blood samples taken before and about 3 to 4 weeks, 7–8 weeks and 4 months after vaccination. Nine healthy subjects were compared with 17 NoEpo and 17 patients with Epo. The average ages were 59.5, 61.3, and 73.1 years, and in those the Epo patients were older. In the healthy group, the percentage of those who support only a partial (double) response, a strong response (four times larger), and an ensemble the response (partial and strong responses combined) were 31.6%, 57.9%, and 89.5%, respectively.

In the NoEpo group, the values were 35.3%, 17.6%, and 52.9%, respectively. In the Epo group the results were similar to those of healthy controls: 23.5%, 58.8%, and 82.4%, Epo vs. NoEpo [20].

Hematological patients (NoEpo group) respond poorly to the influenza vaccine compared to healthy subjects and rHuEpo treatment is associated with an improved immune response to influenza vaccine in patients with hematologic with similar titers in those of healthy subjects [20].

4. **Effects of EPO substitutes on blood viscosity**

Previous study suggests that in hemodialysis patients rHuEPo enables raising the hematocrit to 0.35 with correction of bleeding time without causing intravascular hemostatic activation. Shortening of bleeding time with rHuEPo appears to be due to the hemostatic effects of an increased number of red blood cells, rather than changes in intrinsic platelet function [21] .

Because of the known side effect of rHuEpo in blood coagulation, a study performed a prospective, placebo-controlled, randomized, double-blind trial to determine the effects of intravenous rHuEpo of 200 U/kg daily for 3 consecutive days. They recorded measures of platelet, endothelial cell activation, soluble Fas ligand, and peripheral blood mononuclear cell expression of angiogenesis signaling proteins in 44 subjects with acute myocardial infarction (AMI) treated with aspirin and clopidogrel after successful percutaneous coronary intervention.

The study that evaluated safety and efficacy markers relevant to the biological activity of rHuEpo in patients with AMI concluded that short-term administration of rHuEpo did not alter markers of platelet and endothelial cell activation thrombosis associated. It did increase expression of angiogenesis signaling proteins in peripheral blood mononuclear cells when compared with placebo. Erythropoietin attenuates myocardial lesions and improves ventricular performance after experimental ischemic injury [22]. Recent evidence shows that severe coronavirus disease 2019 (Covid-19) may be complicated with coagulopathy as disseminated intravascular coagulation, which has a rather prothrombotic character with high risk of venous thromboembolism. Present recommendations suggest that all hospitalized COVID-19 patients should receive thromboprophylaxis, or full therapeutic-intensity anticoagulation if such an indication is present [23]. The American Society of Hematology recommends for all hospitalized Covid-19 patients thromboprophylaxis with low molecular weight heparin or fondaparinux (suggested over unfractionated heparin to reduce contact), unless bleeding risk is higher than the thrombosis risk. Despite the lack of present published research, the protocols concerning the strategy for thromboprophylaxis are based on previous clinical experience [24]. In conclusion, the risk of thrombosis as a possible side effect of

rHuEpo therapy can be abolished by the prophylactic use of anticoagulant therapy among Covid-19 patients.

DISCUSSIONS

Dosage of Epo substitute

In a safety and pharmacokinetic study, Wu et al. [25] compared four different Epo dosing regimens (250, 500, 1000 and 2500U/kg, six doses, 48-hour intervals) to 24 newborns who experienced hypothermia for hypoxic-ischemic encephalopathy. The authors found that Epo 1000 U/kg/dose produces optimal neuroprotective levels comparable to animal models, while 500 U/kg/dose produces insufficient neuroprotective levels and 2500U/kg/dose produces levels that exceed the optimal neuroprotective range by approximately three times. Also, in another pharmacokinetic study, the authors found that weekly administration of darbepoetin α produces sufficient serum Epo concentrations. Zhu et al. evaluated two different Epo dosing regimens, 300 U/kg/dose, and 500 U/kg/dose, and found similar clinical effects. Similarly, no differences were observed with the two dosing regimens of darbepoetin α in the study by Baserga et al [26]. It is not known whether the clinical implications are substantial with a high dose (1000 U/kg/dose) compared to the lower dose (300–500 U/kg/dose). Further research is needed to understand the ideal dose at which maximum clinical benefit with minimal or no side effects is seen, as well as a head-to-head comparison of the efficacy of αbepoetin with Epo [18]. Routine use of sc rather than iv rHuEpo to manage anemia in hemodialysis patients could increase survival and reduce hospitalizations for cardiovascular complications by minimizing the dosage of rHuEpo [27].

Epo and Covid-19

A recent article presents the improved results after using rHuEpo in a Covid-19 patient with associated anemia [28]. The patient was 80 years old and had a medical history of Alzheimer's disease and depression. Adjuvant to the Covid-19 treatment protocol, the detected anemia was treated with transfusion of one unit of packed red blood cell (1 day) and rhEpo (300 IU/kg divided into 5 doses of 4000 IU subcutaneous injections in days 1,3,5 and 7). The lab data improvements are presented in **Table 2**[28].

Table 2. Blood tests results in a Covid19 patient with anemia and rhuEpo treatment from[28]

	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7	Day 8
Hb(g/dl)	5.2	6.7	7.9	8.2	7.6	8.6	8.5	9
Neutrophil/uL	5562	5776	7331	9718	6020	6288	4482	4590
Lymph (uL)	333	933	958	893	809	748	588	648
Neutr/Lymph	16.7	6.19	7.65	10.88	7.44	8.41	7.62	7.08

CONCLUSIONS

Substitutes of Epo administered to Covid 19 patients may have a beneficial impact in blood oxygenation in addition to the severe inflammatory reaction due to viral replication. Also, it demonstrated the role in the protection of organs, including brain in brain hypoxia, heart protection in cardiac ischemia and renal protection.

The medical dosage is established based on kg/body, type of the Epo substitute selected and the route of intravenous or subcutaneous administration. The subcutaneous route has greater benefits and low risks. Regarding the thrombosis risk, it can be overcomed by the use of thromboprophylaxis therapy among Covid-19 patients.

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