REVIEW

Iron and Erythropoiesis – Optimizing the Link

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Abstract

Purpose of review: The aim of this paper is to provide the clinician an overview about the link between iron homeostasis and erythropoiesis and how we can promote this relationship in order to improve surgical patients' outcome. **Key elements:** Iron is essential for various cellular processes, like cell signalling, oxygen transport, erythrocyte and heme synthesis, mitochondrial respiration, host defence, nucleic acid replication. Erythropoietin and iron are the main erythropoiesis regulators. Under iron-restricted conditions, the erythrocytes production is impaired, leading to microcytic hypochromic anemia appearance. Iron-restricted condition enables patient capacity to recover from post-surgery anemia. Long-term consequences of chronic anemia affect patient's quality of life. Therefore, parenteral iron supplementation, in patients with anemia secondary to blood loss, can lead to a fivefold increase in erythropoietic response, therefore enhancing recovery. **Summary:** Under normal circumstances, the link between iron and erythropoiesis is maintained especially through regulatory feedback mechanisms, with minimal external support. In face of important blood loss, with secondary acquired iron-restricted anemia, parenteral iron supplementation improves the bone marrow erythroid response and helps correcting haemoglobin levels.

Keywords: iron, erythropoiesis, haemoglobin, macrophage, anemia, surgery.

Rezumat

Scopul recenziei: Scopul acestei lucrări de specialitate este de a oferi clinicianului o analiză sintetizată a legăturii dintre homeostazia sistemică a fierului și eritropoieză, precum și a modalităților de optimizare a acestei legături, cu scopul îmbunătățirii evoluției perioperatorii a pacienților anemici. **Elemente cheie:** Fierul este un element esențial pentru numeroase procese celulare, precum semnalizarea celulară, transportul oxigenului, sinteza eritrocitelor și a grupărilor hem, respirația mitocondrială, apărarea gazdei, replicarea acizilor nucleici. Eritropoietina și fierul sunt principalii reglatori ai eritropoiezei. În condițiile restricției de fier, producția de eritrocite este afectată și apare anemia hipocromă microcitară. Astfel, capacitatea pacienților de a se recupera din anemia post-operatorie este afectată. Consecințele pe termen lung le afectează calitatea vieții. Așadar, administrarea de fier intravenous la pacienții ce dezvoltă anemie după pierderi importante de sânge crește răspunsul eritropoietic și favorizează recuperarea. **Concluzii:** În condiții normale, legătura dintre fier și eritropoieză este menținută prin mecanisme reglatorii de feedback, cu aport extern minim. Dar, în contextul pierderilor importante de sânge, cu anemie secundară prin deficit de fier, suplimentarea parenterală a fierului îmbunătățește răspunsul eritroid al măduvei osoase hematogene și ajută la corectarea anemiei.

Cuvinte cheie: fier, eritropoieză, hemoglobină, macrofage, anemie, intervenție chirurgicală.

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BACKGROUND

The aim of this paper is to provide the clinician an overview about the link between iron homeostasis and erythropoiesis and how we can promote this relationship in order to improve surgical patients' outcome. To be able to correct perioperative anemia in a proper way, it`s important to understand the molecular mechanism behind its appearance. Most of the patients develop anemia after a major surgical intervention and it is largely corrected through blood transfusions. If we remember the main steps of erythropoiesis and its determinants, we will be capable to find alternatives to blood transfusion.

KEY POINTS

1. The normal level of body iron is mainly maintained through senescent erythrocytes recycling.
2. Iron is required for basal cell functioning being involved essentially in hemoglobin and myoglobin synthesis.
3. Erythropoiesis has two important phases: EPO-dependent part and IRON-dependent part.
4. Iron-restricted erythropoiesis leads to hypochromic microcytic anemia.
5. Parenteral iron supplementation in face of important blood loss can lead to fivefold increase in erythropoietic response.

SYSTEMIC IRON HOMEOSTASIS

There are about 3 to 5 g of iron in human body, only 10-30 μmol/l representing the plasmatic levels. Approximately two-thirds of the body iron is bound to haemoglobin and about one-quarter is stored. The organism requires around 25 mg of iron for daily processes[1]. It is provided by the macrophages of the reticuloendothelial system, through daily braking down of all the senescent erythrocytes. Only a limited part comes from nutrition through duodenal absorption. Iron is essential for various cellular processes, like cell signalling, oxygen transport, erythrocyte and heme synthesis, mitochondrial respiration, host defence, nucleic acid replication[2,3].

Over the years, studies have shown that there is no physiological mechanism involved in regulating the iron loss. Therefore, iron hemostasis is maintained through regulatory feedback mechanisms, involving the systemic needs and the intestinal absorption. The main factors responsible for stimulating or inhibiting iron absorption are the iron stores and needs, the erythropoietic activity, the blood haemoglobin and oxygen contents, hypoxia, the level of inflammatory markers[4].

Regarding iron absorption, it is obtain from diet, especially animals, under haemoglobin or myoglobin form. It take place near the gastro-duodenal junction, where the epithelium has villous structure (brush border) with increased absorbing capacity. Dietary iron is converted by ferrireductases to $Fe2^{+}$, transported across the membrane by divalent metal transporter 1 (DMT1), and ferroportin transfers it to the systemic circulation[5-7]. After absorption, iron is bound by transferrin (TF), which in normal state carriers all serum iron, making it soluble and without reactive capacity. The TF saturation is about 30%, varying over time and under local factors influences[8,9].

After the old and deteriorated erythrocytes phagocytosis by tissues macrophages, the released iron is exported to circulatory TF, stored in macrophages or hepatocytes. However, iron overload can lead to hepatotoxicity with secondary fibrosis and cirrhosis[8].

Another protein involved in iron homeostasis is ferritin, a 24-subunit polymer with a cage-like structure, which can store about 4500 iron atoms. Ferritin can accept excess iron or can mobilize it when there is an increased need[10]. Iron regulatory proteins (IRPs) are also involved in controlling iron storage or transport 8.

Hepcidin, a protein compound of 25 amino acids has a major function in iron systemic regulation. In response to increases circulatory iron or overload, persistent inflammation it is highly expressed, but diminished in response to hypoxia, anemia, iron deficiency and increased erythroid activity[11]. Hepcidin hepatocyte production is controlled by acute changes in tissues or plasma iron content[12].

ERYTHROPOIESIS – PRINCIPAL STEPS AND DETERMINANTS

Erythropoiesis, continuous generation and maturation of red blood cells starting from the multipotent stem cells, takes place into the bone marrow. This process can be divided into two major parts. The first part is erythropoietin (EPO) dependent and involves the proliferation and maturation of burst-forming unit-erythroid (BFU-E) and colony-forming unit-erythroid (CFU-E) from the megakaryocyte-erythrocyte progenitor. The second part is iron dependent, involving the differentiation of proerythroblasts into mature red cells[9,13].

Therefore, EPO, a glycoprotein hormone produced by cells of renal cortex, is the main erythropoiesis regu-

lator, preventing apoptosis. Iron, the second erythropoiesis regulator, is vital for haemoglobin synthesis, transferrin being the main source for the erythroid cells[14].

The daily erythrocytes production is around 200 billion requiring 25 mg of iron for the bone marrow. As we have emphasized before, the majority of this is obtained through erythrocytes recycling, in the absence of anemia, and minimal intestinal absorption[15].

IRON-DEPENDENT AND IRON-RESTRICTED ERYTHROPOIESIS

Iron deficiency is the leading cause of anemia, affecting millions of people. In surgical patients, this condition leads to an improper recovery with long-term consequences. Under iron-restricted conditions, the erythrocytes production is affected, being smaller than normal (microcytic) and containing a lower haemoglobin concentration (hypochromic)[14].

The bone marrow is the most important iron user in erythroid processes. About two-third of the total iron is utilized for the production and maturation of red blood cells and near to a billion atoms are incorporated to form haemoglobin in this new erythrocytes. Erythroid precursors present on the surface transferrin receptors (TFRs) through which it captures, by endocytosis, the Fe-TF complex[8,16].

Under normal circumstances, bone marrow is able to maintain the erythropoiesis in a steady state. However, in times of anemia, stress erythropoiesis is activated in order to ensure normal tissues and cells oxygenation. Animal studies have shown that this process can become extramedullary, taking place in spleen or liver through migration of the short-term reconstituting hematopoietic stem cells (ST-HSCs)[17].

Patients facing an important blood loss have an accelerated bone marrow erythropoiesis to restore erythrocytes number and oxygen carrying capacity. Therefore, the iron delivery and consumption is maximum. Under iron-restricted conditions, patient capacity to recover from anemia is blunted, leading to an impaired rehabilitation after surgery[18]. Intravenous iron therapies correct haemoglobin levels by reducing iron-restricted erythropoiesis. Studies have shown that free iron resulting from blood transfusion increase the risk of infections and oxidative stress[19].

PRACTICAL ASPECTS

The main cause of iron deficiency is blood loss, with each millilitres of lost blood, around 0.5 mg of iron being also lost. Therefore, most of the surgical patients, especially those who underwent major surgery, may develop acquired iron deficiency anemia. It is defined by some specific laboratory exams presented in Figure 1. Bone marrow biopsy represents the gold-standard of diagnosis, but in clinical practice it is rarely performed being an invasive, painful and hard to tolerate manoeuvre[20].

Figure 1. Defining laboratory exams for iron deficiency anemia (hypochromic microcytic anemia)

Serum biomarkers	Value
Haemoglobin	< 11 g/dL
Serum ferritin	< 0.4 mg/L
Transferrin saturation (TSAT)	< 16%
Serum iron	< 60 mcg/dL
MCH (mean corpuscular haemoglobin)	< 26 pg
MCV (mean cell volume)	< 70 fL

Iron represents the fuel for erythropoietin (EPO), which stimulates the bone production of red blood cells and the response to anemia, these two elements modulating the erythropoiesis[20]. Nowadays, there are some methods used for preventing or correcting the perioperative anemia.

The recombinant human erythropoietin (r-HuEPO) is used to correct preoperative anemia or to prevent it`s development after a major surgery, especially in patients with chronic renal failure[21]. Over the years, studies have showed a positive response in 95% of anemic patients. In orthopaedic surgery, there was a period when autologous blood donation was a high standard of medical care. Therefore, r-HuEPO represented an alternative to make this process possible knowing that it can be performed in patients with a haematocrit value more that 33% and a haemoglobin above 11 g/dL or to correct the anemia secondary to autologous donations. r-HuEPO can also be used for patients who refuse transfusions due to various motivation[20,22]. The recommended dose is 250-300 UI/kg twice a week, for three weeks before/after surgery, administered subcutaneous (more physiological compared to the intravenous administration). It is important to determine the endogenous EPO in all anemic patients prior to the treatment. Studies shows that the interval between administrations should be about 72 hours to obtain a greater erythropoietic response and it should be combined with intravenous iron administration[23].

Over the last decade, the use of parenteral iron in perioperative period, with the intent of correcting anemia

Figure 2. Frequently used parenteral iron formulas and dosage

Parenteral iron formula	Dosage	Comments
1. Iron isomaltoside 1000 (Monofer®)	20 mg/kg	- three times a week administration regimen
2. Ferric carboxymaltose (Ferinject®, Injectafer®)	1000 mg (body weight 35-70 kg) 1500 mg (body weight >70 kg)	- maximum dose 20 mg/kg
3. Iron sucrose (Venofer®)	200 mg	- one week administration, four-weeks regimen

and preventing blood transfusions, was intensively studied. Anemia and blood transfusion are associated with increased risk of mortality and morbidity in surgical patients, especially through decompensation of chronic diseases[24]. The newest intravenous formulations are associated with low risk of adverse events appearance. Some clinical manifestations, like fever, myalgias or arthralgias can appear secondary to iron toxicity in cases with transferrin saturation above 100%, but with proper administration and close monitoring these are rare circumstances. In surgical patients, iron deficiency can be real, due to excessive iron use for producing erythrocytes, with subsequent iron stores depletion, or can be a functional deficiency, when the high demand cannot be satisfied by a normal supply. Therefore, parenteral iron supplementation, in patients with anemia secondary to blood loss, can lead to a fivefold increase in erythropoietic response[25-27]. In Figure 2 are presented some of the usual iron formulas used in clinical practice and the normal dosage[28,29].

SUMMARY

Iron, erythropoietin and erythropoiesis are interconnected. Under normal circumstances, and in patients without chronic conditions, this link in maintained especially through regulatory feedback mechanisms, with minimal external support. The main disruptive element in surgical patients is important blood loss that enables the organism to overcome the increased iron requirements. Apart from blood transfusion, which can produce reactive iron species, parenteral administration represents the gold standard of medical care, being well tolerated and with low risks of adverse events, ensuring a rapid improvement of patients anemic status and outcome.

Compliance with ethics requirements: The authors declare no conflict of interest regarding this article. The authors declare that all the procedures and experiments of this study respect the ethical standards in the Helsinki Declaration of 1975, as revised in 2008(5), as well as the national law. Informed consent was obtained from all the patients included in the study.

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