

Commentary

Role of iron in anaemic critically ill patients: it's time to investigate!

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Abstract

Anaemia is a common problem in critically ill patients admitted to intensive care units. Many factors can be involved in its development, including rapid alterations in iron metabolism. Maintenance of iron homeostasis is a prerequisite for many essential biological processes and is a central element for the development of erythroid precursors and mature red blood cells. With the inflammatory process, iron distribution is disturbed, with decreased serum iron levels and increased iron stores. Little information is available on the precise role of alterations in iron metabolism in the development of iron anaemia in critically ill patients.

Keywords anaemia, erythropoietin, iron, red blood cell

Anaemia is a major cause of morbidity and mortality worldwide and is often observed in critically ill patients, not just at admission but particularly during intensive care unit (ICU) stay [1]. The time course of anaemia during an ICU stay depends on the underlying pathologies [1], but at least a third of ICU patients receive a transfusion at some point during their ICU stay [2,3]. The rationale behind blood transfusion is to restore oxygen delivery and provide a reserve should further bleeding occur. Several recent studies have modified transfusion practice, in terms of the level of pretransfusion haemoglobin concentration [3] and in view of the adverse effects of blood transfusion, including haemodynamic and immunomodulatory effects, and transmission of micro-organisms [2,3].

The aetiology of anaemia is often multifactorial, including overt or occult blood loss (e.g. resulting from frequent blood sampling or surgical procedures), haemodilution, reduced red blood cell (RBC) production caused by decreased synthesis of endogenous erythropoietin (EPO), and probably also reduced RBC lifespan due to increased uptake by the

reticuloendothelial system [4,5]. Alteration in iron metabolism plays a central role in the development of anaemia [6]. The majority of the body's iron content is incorporated into haemoglobin in developing erythroid precursors and mature RBCs, but this process is rapidly altered with the acute phase reaction. Typically, the inflammatory process is associated with low concentrations of serum iron, high ferritin (the protein responsible for iron storage), and low transferrin (the principal iron transporting glycoprotein) [7]. The underlying mechanisms are very complex and not well understood, although the final teleological aim is primarily to deprive bacteria of nutritionally required iron. In fact, in just a few hours, proinflammatory and anti-inflammatory cytokines cause a decrease in the iron level in blood.

Proinflammatory cytokines such as tumour necrosis factor- α , IL-1 β and IL-6 induce the transcription and the translation of ferritin; modulate the binding affinity of cytoplasmic iron regulatory protein (IRP)-1 and IRP-2, which contain iron-responsive elements; and rapidly decrease the mRNA expression of transferrin receptor [8]. Interferon- γ stimulates

iron absorption by enterocytes via the divalent metal transporter-1, but it has an inhibitory effect on ferroprotein – another enterocyte protein that transfers oxidized iron into the circulation. These alterations result in increased iron storage in enterocytes [9]. Anti-inflammatory cytokines such as IL-4, IL-10 and IL-13 induce haem oxygenase-1 expression to promote haem degradation and iron storage in monocytes and thereby contribute to iron storage in the reticulo-endothelial system [10]. Nitric oxide reduces RBC production by stimulating IRP and reducing ferrochelatase activity, which inhibits the final step in heme synthesis [11].

In the present issue of *Critical Care*, Darveau and coworkers [12] review the literature on iron supplementation in anaemic critically ill patients. That article reveals the lack of studies evaluating alterations in iron metabolism in ICU patients. Darveau and coworkers [12] also provide a summary of studies using EPO therapy, the rationale behind this strategy in anaemic ICU patients being that EPO levels are inappropriately low [6] as a result of the effects of proinflammatory cytokines (interferon- γ , tumour necrosis factor- α , IL-1) that inhibit EPO receptors on erythroid progenitor cells. In randomized, double-blind, placebo-controlled studies, Corwin and coworkers [13,14] demonstrated the safety of EPO treatment plus iron administration and the resulting decrease in number of RBC transfusions needed, but regrettably they reported no effects on outcome in terms of ICU infection rates or mortality. Only one study [15] compared the effect of iron administration (20 mg/day intravenously) with that of treatment with EPO (300 mg subcutaneously on days 1, 3, 5, 7 and 9) and iron. Surprisingly, in that study the reticulocyte count increased significantly at day 6 in the EPO-treated group as compared with the iron and control groups, but it rapidly decreased thereafter, with no apparent difference between groups at day 18. Moreover, there were no differences in ICU length of stay or the total number of RBC transfusions after 3 weeks between the iron and EPO groups. Although the number of patients was limited, this is probably the only study comparing iron administration and EPO therapy in the ICU. Importantly, both treatments have possible side effects: for EPO treatment, anti-EPO antibodies with severe aplasia [16], transient alterations in RBC rheology [17] and anaemia secondary to cessation of intensive treatment [18]; and for iron administration, anaphylactoid reactions with increased risk for infection [7].

As highlighted by Darveau and coworkers [12], before supplementing critically ill patients with iron we need additional studies to investigate and better define the role played by iron, including the place of primordial regulators of iron metabolism such as hepcidin and transferrin receptor [19,20], in the development of anaemia in this population.

Competing interests

The authors declare that they have no competing interests.

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