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POINT OF VIEW

Is there a role for iron supplementation in critically ill patients?

Suplementos de hierro: ¿son útiles en el paciente crítico?

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Anemia is the most common hematological disorder among patients admitted to the intensive care unit (ICU). The majority of critically ill patients presented with anemia upon ICU admission (up to 30% with hemoglobin <10 g/dL), which tends to persist throughout the duration of their ICU stay and for many weeks after ICU discharge, unless modified by red blood cell transfusions (RBCT).[1] Though the etiology of anemia of critically ill patients is multifactorial and complex, iron restricted erythropoiesis, due to absolute iron deficiency or hepcidin-induced iron sequestration with decreased iron availability (functional iron deficiency), is commonly involved in its induction and persistence.[1]

The most important consequence of anemia is a decreased oxygen delivery to tissues. While mild anemia does not seem to adversely affect patient's outcome, severe anemia may result in a 50% increase in the odds ratio of mortality, though RBCTs also result in a dose-dependent increase of mortality risk (up to 4-fold when more than 4 RBCT units are administered).[2] Even when used with restrictive criteria, patients receiving RBCT have poorer clinical outcomes.[3] Therefore, severe anemia should be avoided, corrected or, at least, ameliorated before oxygen delivery and consumption are impaired, and RBCT needed.

Additionally, non-anemic patients with reduced or absent iron stores may have symptoms such as fatigue or reduced exercise tolerance, as recently reported for patients discharged after prolonged ICU stay.[4] In congestive heart failure, iron deficiency was also independently associated with compromised physical performance and quality of life, and an increase of cardiovascular and all-cause mortality; in contrast, treatment of iron deficiency with intravenous iron have been shown to improve short- and long-term functional status.[5]

To avoid the development and/or progression of anemia in non-bleeding ICU patients, reduction of blood losses (reduction in diagnostic phlebotomy frequency and volume, use of in-line closed blood conservation devices, cell salvage during surgical procedures, etc.) and pharmacologic stimulation of erythropoiesis should be attempted. The administration of erythropoietin emerged as a promising therapeutic option. However, when a restrictive transfusion protocol was in place, a reduction in RBCT was not consistently demonstrated, except for one randomized trial in which adjuvant intravenous iron was associated with erythropoietin.[1] Failure of erythropoietin treatment in reducing RBCT may have been related to inadequate iron supplementation. Thus, laboratory definitions for

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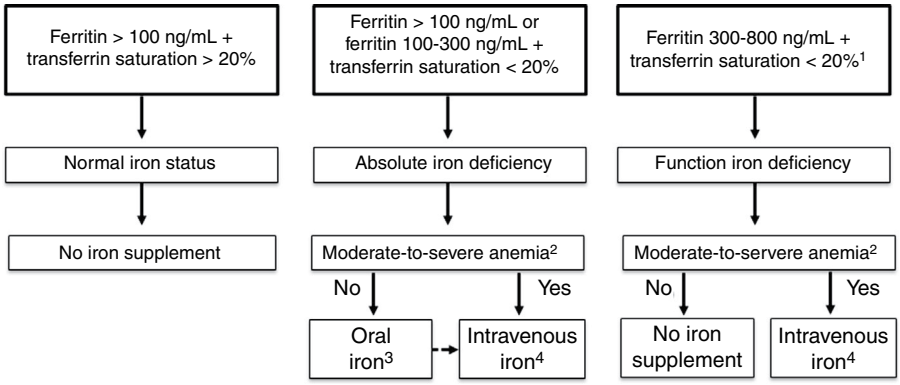

Figure 1 A tentative algorithm for management of iron deficiency in critically ill patients.
1. The presence of iron deficiency can be confirmed by reticulocyte content (<28 pg), percentage of hypocromic red cells (>5%), or ferritin index >2.
2. Moderate-to-severe anemia: hemoglobin <11 g/dL.
3. Low dose (30–60 mg/day) of newer oral iron formulations, such as sucrosomial iron, could be preferred. Switch to intravenous iron if intolerance to or lack of efficacy of oral iron.
4. Iron sucrose (100 mg/48 h) or ferric carboxymaltose/iron isomaltoside/low molecular weight iron dextran (500 mg/week). IVI administration should be discontinued if there is evidence of iron overload, as indicated by serum ferritin ≥1000 ng/mL or transferrin saturation ≥50%.

absolute and functional iron deficiency, as well as doses and routes of iron supplementation should deserve especial attention.

Accurate diagnosis of iron restricted erythropoiesis is essential before initiating iron supplementation. However, diagnosis of iron deficiency at ICU is difficult as ferritin levels may be elevated as part of the inflammatory response in ICU patients. A ferritin <100 ng/dL indicates insufficient iron stores to support erythropoiesis in the setting of anemia and inflammation (e.g., C-reactive protein >5 mg/L) which is common among ICU patients. Further markers for absolute iron deficiency are transferrin saturation <20% with ferritin concentrations of 100–300 ng/mL, reticulocyte hemoglobin content <28 pg, hypochromic red cells >5% or ferritin index >2[6] (Fig. 1). The ferritin index is the ratio between the serum-soluble transferrin receptor and the logarithm of serum ferritin.[6] Ferritin concentrations >300 ng/mL with transferrin saturation <20% are indicative of functional iron deficiency. These values and parameters may signal the need for intervention, as parameters of the

Table 1 Characteristics of different intravenous iron formulations available in Spain.

	Iron[a] sucrose	LMWID[b]	Ferric[c] carboxymaltose	Iron[d] isomaltoside
Brand name	Venofer®	Cosmofer®	Injectafer® Ferinject®	Monofer® Monoferro®
Molecular weight (kD)	30–60	165	150	150
Labile iron (% injected dose)[e]	3.5	2.0	0.6	1.0
Maximal single dose (mg)	200	20 mg/kg	20 mg/kg (max 1000 mg)	20 mg/kg
Suggested dosage in ICU patients:				
Dose (mg)/frequency (days)	100/2	500/7[f]	500/7	500/7
Infusion time (min)	30	60	15	15
Maximal total dose (mg)	2000	2000	2000	200
Product cost per 1000 mg (€)[g]	112	103	192	192

[a] Venofer summary of product characteristics. http://www.luitpold.com/documents/22.pdf (accessed 18.02.18).
[b] LMWID, low molecular weight iron dextran; Cosmofer summary of product characteristics. http://www.cosmofer.com/product/cosmofer-spc/cosmofer-spc.aspx (accessed 18.02.18).
[c] Ferinject summary of product characteristics. http://www.ferinject.co.uk/smpc/ (accessed 18.02.18).
[d] Monofer summary of product characteristics. http://www.monofer.com/spc.aspx (accessed 18.02.18).
[e] Jahn MR, et al. Eur J Pharm Biopharm 2011; 78:480–91.
[f] Although it is not an approved dosing by European Medicines Agency, Auerbach et al. (Am J Hematol 2011; 86: 860) have not observed any serious adverse events in over 5000 administration of LMWID at doses of 1000 mg in 250 mL of normal saline over 1 h.
[g] Quintana M, et al. Blood Transfus 2017; 15:438–46.

Table 2 Randomized controlled trials evaluating the effect of iron administration in ICU patients (6 studies, 660 patients).

Study reference setting	Patients	Baseline Hb (g/dL)	Iron compound dose (mg)	RBCT (% or units)	Infection (%)	Mortality (%)	Hospital stay (days)
Madi-Jebara et al.[a]	IS:40	9.9	IS (437 mg)	25%	?	?	?
J Cardiothorac Vas Anesth 2004;18:59–63.	IS+EPO: 40	10.2	IS (402 mg) + EPO(300 U kg^{-1})	17%	?	?	?
Cardiac surgery	Placebo: 40	10.8		22%	?	?	?
Karkouti et al.[b]	IS:11	8.5	IS (600 mg)	18%	?	?	?
Can J Anaesth 2006; 53:11–9.	IS+EPO: 10	8.3	IS (600 mg) + EPO (900 U kg^{-1})	20%	?	?	?
Cardiac & orthopedic surgery	Placebo: 10	8.3	All with oral iron after discharge	40%	?	?	?
Garrido-Martín et al.	IS:54	10.5	IS (300 mg preop + 300 mg postop) + oral after discharge	37%	?	?	?
Interact Cardiovasc Thorac Surg 2012; 15:1013–8.			105 mg day^{-1} preop, postop and after discharge				
Cardiac surgery	Oral iron:53	10.7	105 mg day^{-1} after discharge	51%	?	?	?
	Placebo: 52	10.5		50%	?	?	?
Pieracci et al.[c]	IS: 75	<12	100 mg IV thrice weekly up to 2 weeks	73.3%	58.7	9.3	14
Crit Care Med 2014;42:2048–57.							
Trauma ICU	Placebo: 75	<12		62.7%	69.3	9.7	16
Johanson et al.[d]	ISM:30	10.2	ISM (1000 mg at CPB end or wound closure)	13.3%	10	0	5
Vox Sanguinis 2015; 109:257–66.							
Cardiac surgery	Placebo:30	10.5		20.0%	30	0	5
Litton et al.[e]	FCM: 70	8.9	FCM 500 mg/infusion	54%	28.6	7	15
Intensive Care Med 2016; 42:1715–22			Up to 2000 mg	79 units			
Medical and surgical ICU							
	Placebo: 70	8.7		56% 121 units	22.9	4	18

CPB, cardio-pulmonary bypass; EPO, recombinant erythropoietin; FCM, ferric carboxymaltose; FS, ferrous sulphate; Hb, hemoglobin; ICU, Intensive Care Unit; IS, iron sucrose; ISM iron isomaltoside-1000; IVI, intravenous iron; LOS, length of hospital stay; OBS, observational study; RBCT, red blood cell transfusion.

[a] Randomization bias Hb levels: in the control group Hb were significantly higher than these observed in the treated groups.

[b] It was estimated a priori that 20 patients in each group would be sufficient to detect an incremental increase in Hb of 0.8 g/dL. A total of 3473 patients were screened. Of the 140 eligible patients, 102 refused to participate and 38 were randomized, and primary outcome was available in 31.

[c] In subgroup analysis, also no benefit was observed for those receiving all 6 doses of iron sucrose or placebo. Follow-up 42 days or discharge.

[d] Hb levels at postop day 5. One month after surgery, significantly more patients were non-anemic in the intravenous iron isomaltoside 1000-treated group compared to the placebo group (38.5% vs. 8.0%; $p = 0019$).

[e] 70% surgical patients. Inclusion criteria Hb <10 g/dL, ferritin <1200 ng/mL, transferrin saturation <50%. Most patients received a total of 500 mg FCM. Only 15 patients received 2 doses, and only 2 patients received 3 doses.

iron status, but not anemia per se, independently influence transfusion rate, complications and in-hospital mortality[7] (Fig. 1).

High dose oral ferrous sulfate (325 mg thrice daily; approx. 300 mg elemental iron/day) has been shown to reduce RBCT requirements in critically ill patients with iron deficiency, though there was not a formal transfusion protocol.[8] Recent evidence from the IRONOUT study in patients with chronic heart failure further supports the ineffectiveness of oral iron in the setting of inflammation.[9] However, oral sucrosomial iron has an absorption mechanism which is mostly hepcidin-independent, and its administration at low doses (30–60 mg) has been shown effective in clinical settings (e.g., chronic kidney disease) where intravenous iron seemed to be the only treatment option.[10] A possible role of sucrosomial iron needs to be tested in ICU patients.

Some characteristics of available intravenous iron formulations in Spain are depicted in Table 1. The total iron dose (TID) is calculated according to: TID = body weight (kg) $\times$ 2.4 $\times$ hemoglobin deficiency (target hemoglobin level $-$ patient hemoglobin level; g/dL) + 500–1000 mg (repletion of iron stores). For the approved indications and at recommended doses, all available ''original'' intravenous iron formulations are essentially equal in terms of safety and efficacy.[11] However, when administering intravenous iron, more stable formulations with low labile iron content (e.g., ferric carboxymaltose or iron isomaltoside) could be preferred to avoid oxidative stress,[11] though drug acquisition costs are considerably higher. Maximal single dose will depend on the available compound, but we suggested lower single dosing schedules (Table 1). Iron status should be checked weekly, and intravenous iron administration discontinued if there is evidence of iron overload, as indicated by serum ferritin $\geq$1000 ng/mL or transferrin saturation $\geq$50%. In patients receiving ferric carboxymaltose, phosphate levels should be periodically monitored for early detection and management of hypophosphatemia.[11]

The analysis of 6 randomized trials on iron supplementation in adult critical care with 860 patients found no difference in RBCT or hemoglobin, except in two trials (Table 2). These two trials involved the administration of iron isomaltoside IV to non-anemic patients at the end of cardiac surgery or oral iron to critically ill surgical patients with iron deficiency on admission. There was also no difference in secondary outcomes of mortality, in-hospital infection, or length of stay (Table 1). However, there was considerable heterogeneity between trials in study design, populations, interventions, and outcomes, and administered intravenous iron doses may have been insufficient to meet patents' needs (Table 2). In addition, doses were substantially lower than in the REPAIR-IDA trial of intravenous iron to treat iron-deficiency anemia in non-dialysis-dependent chronic kidney disease (ferric carboxymaltose 1500 mg vs. iron sucrose 1000 mg), where clinically significant increments on hemoglobin levels were observed.[12]

Thus, more well-designed trials are required to ascertain which ICU patients are more likely to benefit from these treatments in terms of patient-focused outcomes, as well as to identify the optimal doses and administration schedules. Meanwhile, because of the absence of definitive clinical data, it seems reasonable to limit total intravenous iron dose to 2000 mg, and to avoid its administration in patients with hyperferritinemia (>800 ng/mL) or in the setting of acute infection, especially in sepsis.[11]

Conflict of interests

Manuel Muñoz has received industry-supplied funding for consultancies, lectures and/or travel from Pharmacosmos, Vifor Pharma, Zambon, Pharmanutra, Sandoz and Celgene, and is member of the editorial board of Revista Española de Anestesiología y Reanimación and Blood Transfusion. Susana Gómez-Ramirez has nothing to declare.

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