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Preoperative Phase – Preoperative management of the patient's anemia

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ABSTRACT

Managing anemia before surgery is extremely important as it is a clinical condition that can significantly increase surgical risk and affect patient outcomes. Anemia is characterized by a reduction in the number of red blood cells or hemoglobin levels leading to a lower oxygen-carrying capacity of the blood. Proper treatment requires a multifaceted approach to ensure patients are in the best possible condition for surgery and to minimize potential complications. The challenge is recognizing anemia early and implementing a timely intervention to correct it. Anemic patients are more susceptible to surgical complications such as increased infection rates, slower wound healing and increased risk of cardiovascular events during and after surgery. Additionally, anemia can exacerbate existing medical conditions, causing greater strain on organs and organ systems. To correct anemia and optimize patient outcomes, several essential

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measures must be taken with the most common being identifying and correcting iron deficiency.

Preoperative management of anemia

About one third of the world's population has some degree of anemia. The World Health Organization (WHO) defines anemia as Hb <12 g/dL in women and Hb <13 g/dL in men.[1] Iron deficiency is the most common cause of anemia. It can be provoked by increased physiological demand for iron (growth spurts in children, pregnancy in women), low intake (malnutrition, vegetarian or vegan diets), malabsorption (surgical causes, inflammatory disease, celiac disease) and chronic losses (menorrhagia, gastric ulcer, hematuria).[2,3]

The second most common cause of anemia is known as anemia of chronic disease (anemia of inflammation) and is associated with conditions such as neoplasms, chronic diseases (heart failure, kidney failure, chronic obstructive pulmonary disease) and autoimmune diseases. In anemia of chronic disease, there may be a component of functional iron deficiency, in which iron is not available for erythropoiesis. This occurs mainly due to an increase in the hormone hepcidin, which is stimulated by inflammatory cytokines.[1] A small portion of anemia cases are associated with deficiencies in elements such as vitamin B12 and folic acid, due to lack of intake or conditions of malabsorption.[4]

The prevalence of anemia in the preoperative period is around 36 %; this varies according to demographic factors and the underlying disease. Postoperatively, the prevalence of anemia can reach 80–90 %.[5] As in the general population, iron deficiency (ID) is also the most common cause of anemia among patients submitted to surgery, accounting for two thirds of patients.[1] In most cases, the diagnosis of the cause of anemia can be carried out by a non-specialist doctor using laboratory tests that are widely accessible and easy to interpret.[1] After initial assessment, if the cause of the anemia is not obvious, if there is another associated cytopenia (not explained by the underlying disease) or if there is evidence of other mechanisms of anemia, such as the presence of hemolysis, the patient should be referred to a specialist.

Each center must have an algorithm, adapted to its own reality, for the initial investigation of anemia in the preoperative period taking into account the complexity of the patient and the availability of tests. Every protocol must at least include a blood count and an investigation of iron levels (ferritin and transferrin saturation) for patients who will undergo surgery with a risk of transfusion >10 % or an estimated blood loss of >500 mL. Patients with signs or symptoms of anemia, ID or risk factors for both should also be investigated.[1]

Table 1 provides a summary of the usefulness of each test in the investigation of anemia, while Figure 1 is an example of an algorithm for the preoperative approach to anemia by a non-hematologist.

Treatment of iron deficiency

With confirmation of iron deficiency as the cause of anemia, two measures need to be implemented in parallel:

a) Identification of possible bleeding and its cause, if it is not evident and
b) The choice of the replacement therapy most appropriate for each patient and specific context, which can be carried out, in general, using one of the following three approaches:

- oral iron formulations.
- low-dose injectable iron formulations.
- high-dose injectable iron formulations.

To define the best replacement strategy in each specific scenario, it is important to consider factors such as:

- **Intensity of anemia and possible organic repercussions:** Patients with more severe anemia, significant symptoms or with important comorbidities, such as heart disease or ischemic conditions, may not benefit completely from the use of low-dose oral or parenteral formulations due to the longer time necessary to recover erythropoiesis.
- **Interval until the surgical procedure:** Preoperatively, intravenous replacement quickens hemoglobin recovery and should be preferred over oral replacement, especially if the interval before surgery is less than six weeks.[6] However, even with high-dose intravenous iron formulations, an interval of at least 10 days between the infusion and the surgical procedure is recommended to achieve a satisfactory response.[7]
- **Gastrointestinal intolerance:** In addition to limitations in absorption rates (maximum 25–30 mg of elemental iron/day), oral formulations can lead to considerable side effects, such as epigastric pain, heartburn, nausea and intestinal constipation, which can prevent the continuation of treatment in a significant portion of patients. Patients with active inflammatory bowel diseases may also have worsened symptoms.[8]
- Inadequate absorption: For patients with absorption problems (atrophic gastritis, gastrectomy, post-bariatric surgery, etc.) or patients with chronic or inflammatory diseases (renal failure, heart failure, inflammatory bowel disease, etc.) prefer intravenous replacement as in these cases the absorption of oral iron will be low.
- Availability/access: Patients in a more restricted socioeconomic context may have significant barriers to accessing

Table 1 – Usefulness of exams in the initial investigation of anemia.

Exam	Utility		
Complete blood count	Indicates the hemoglobin level (presence or absence of anemia). Allows the evaluation of MCV/ MCH/RDW, which help to identify the type of anemia. Indicates the existence of other cytopenias (leukopenia, thrombocytopenia).	MCV <80 fl (microcytic)	ID, thalassemia, sideroblastic anemia
		MCV 81–95 fl (normocytic)	Chronic disease anemia, combined deficiency (iron + Vitamin B12/folic acid), MDS, hemolytic anemia
		MCV >95 fl (macrocytic)	Vitamin B12/folic acid anemia, alcoholism, cirrhosis, MDS, reticulocytosis (hemolysis) agglutination
Reticulocyte count	When increased, it indicates an attempt by the bone marrow to compensate for the peripheral destruction of red blood cells (hemolytic anemias), that is, erythropoiesis is preserved. A low count suggests impairment of erythropoiesis due to deficiencies: EPO deficiency (CKD), bone marrow failure, hematological neoplasms, among others.		
Ferritin	This is the most specific test and best reflects the body iron deposits. It is widely available and standardized. Serum ferritin <15 mcg/L is confirmatory for ID. A value <30 mcg/L has greater sensitivity (92 %) and a similar specificity (98 %) and is most often used. The presence of inflammation causes ferritin (acute phase protein) to increase, interfering with the assessment of ID. Currently, serum ferritin levels <100 mcg/L are accepted to diagnose ID in chronic inflammatory conditions (this level is also commonly recommended in the elderly and post-operatively). For ferritin levels 100–300 mcg/L in the presence of inflammation, it is recommended to use transferrin saturation (<20 %) in conjunction with ferritin to define ID.		
Transferrin saturation (TS)	Increased hemolytic anemias, inefficient erythropoiesis, megaloblastic anemia. Increased LDH together with an increase in reticulocytes or indirect bilirubin should raise suspicion of hemolysis.		
Haptoglobin	A very sensitive and specific marker for the presence of hemolysis. It binds to free heme and is rapidly removed from circulation, however it is reduced in the presence of hemolysis, including with intramedullary hemolysis observed in megaloblastic anemia. It may be increased in the presence of inflammation, but this increase, in general, is not sufficient to hide hemolysis. It reduces in chronic liver disease.		
Direct antiglobuin test (DAT or direct Coombs)	DAT has low predictive value in the absence of hemolysis. That is, it should not be used in the initial investigation of anemia. It should be requested when there are indications that the anemia is hemolytic, with the aim of investigating whether there is an immune component involved in the destruction of the red blood cells.		
Bilirubin	This is especially useful to evaluate the presence of a hemolytic component in which there may be an increase in indirect bilirubin.		
Vitamin B12 and folic acid measurements	Widely available. Measurement and replacement should be considered in all at-risk patients for these deficiencies (restricted diets, atrophic gastritis, inflammatory bowel disease, etc.) or who will be submitted to procedures with risk of major blood loss.		
Others: Renal function, Glycated Hb, CRP, TSH, enzymes and hepatic function	In the presence of anemia, especially when absolute ID has been ruled out as the cause, it is important to evaluate the presence of other comorbidities and inflammation.		

MCV: Mean corpuscular volume; MCH: Mean corpuscular hemoglobin; RDW: Red cell distribution width; MDS: Myelodysplastic syndrome; EPO: Erythropoietin; CKD: Chronic kidney disease; ID: Iron deficiency; LDH: Lactate dehydrogenase; Hb: Hemoglobin; CRP: C-reactive protein; TSH: Thyroid stimulating hormone.

injectable (especially high-dose) formulations considering the higher cost and the need for an infusion center.

- Venous access: Patients in need of intravenous replacement and with difficult venous access should benefit from the use of high-dose iron, as, in general, one infusion is sufficient for complete replacement.

Table 2 summarizes the main advantages and disadvantages of alternatives for iron replacement.

Oral iron replacement

The dose traditionally recommended for iron replacement is 100–200 mg of elemental iron per day, divided into two to three doses. However, more recent studies have shown that the use of a single daily dose every other day improved the absorbed fraction of iron and reduced adverse effects.[8] Thus, the current trend is to indicate smaller doses of elemental

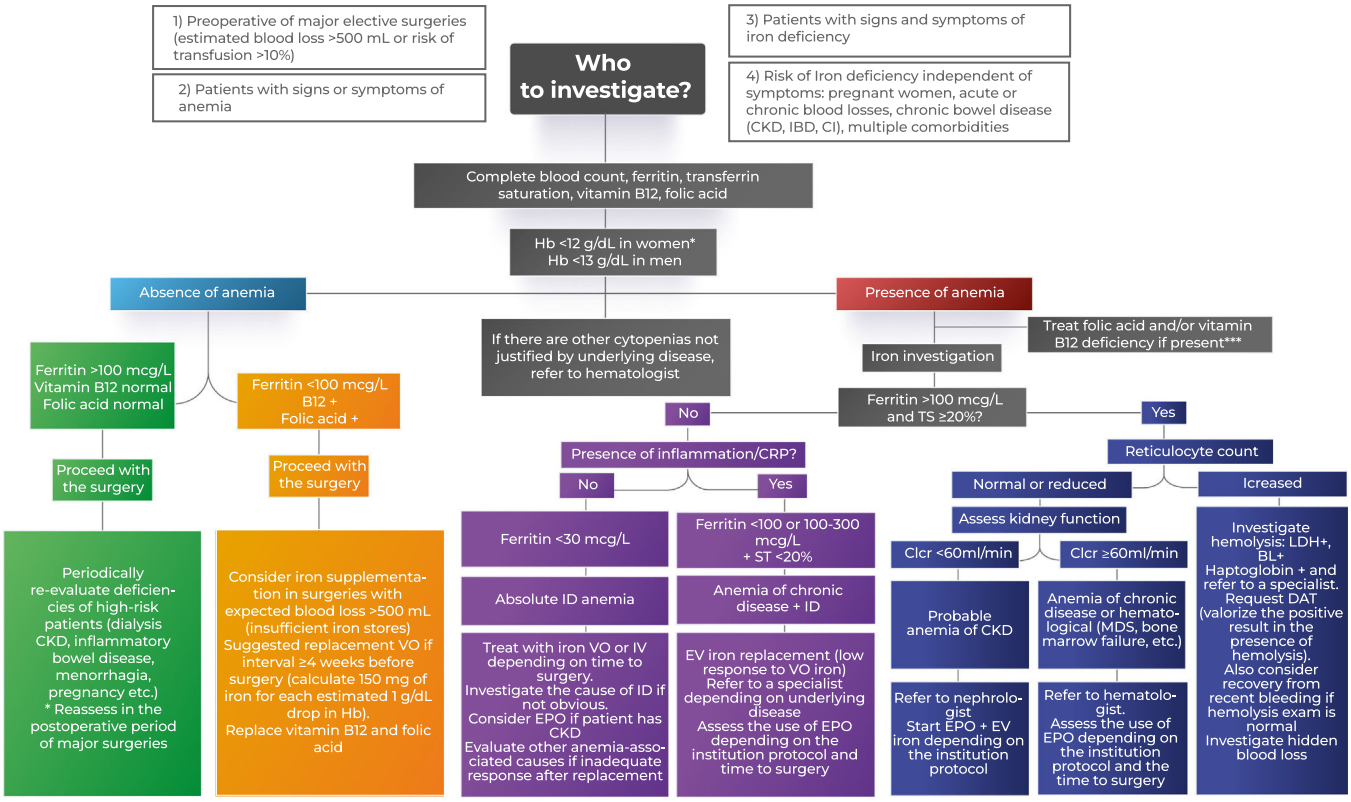

Figure 1 – Algorithm to investigate preoperative anemia treatment.

CKD: chronic kidney disease; IBD: inflammatory bowel disease; CI: Cardiac insufficiency; VO: Via oral; EV: Endovenous; BL: Bilirubin; LDH: Lactate dehydrogenase; TSH: Thyroid-stimulating hormone; ID: Iron deficiency; EPO: erythropoietin; MDS: Myelodysplastic syndrome; CrCl: Creatinine Clearance; CRP: C-Reactive protein; DAT: Direct antiglobulin Test; TS: Transferrin saturation.

Table 2 – Main characteristics comparing oral and parenteral iron formulations.

	Oral	Intravenous
Posology and administration	Easy to administer but requires daily use for long periods	Requires an infusion center, some formulations have the possibility of singe infusions
Absorption	Reduced in inflammatory conditions	Not influenced by inflammation
Gastrointestinal tract effects	Epigastralgia, heart burn, nauseas, intestinal constipation	Rare
Other side effects	Alterations in skin color	Reactions at injection site, headaches, hypophosphatemia with some formulations
Therapeutic response	Limited by the side effects and situations of limited absorption	Faster recovery of Hb levels and iron stocks
Access to patients	Widespread availability, low cost	High-dose formulations with higher cost and necessity of infusion center

Adapted from Cappellini, Musallam KM, Taher (2020).[1]

iron (60–120 mg) in a single daily intake on alternate days.[9] An option also, in case of oral intolerance, is to change the oral formulation, for example, from ferrous sulfate to polymaltose iron. Table 3 shows the elemental iron concentration of some of the oral formulations.

Intravenous iron replacement

Table 4 summarizes the main indications for the use of intravenous iron, while Table 5 describes the characteristics of

Table 3 – Principal oral iron salts.

Iron salt	Presentation	Concentration of elementary iron
Iron sulfate (20 % of elementary iron)	200 mg Tablets/Capsules	40 mg
	400 mg Tablets/Capsules	60 mg
	500 mg Tablets/Capsules	100 mg
	125 mg/mL drops	25 mg/mL
Iron III hydroxide polymaltose complex (30 % of elementary iron)	435 mg Tablets	123 mg
	330 mg chewable Tablets	100 mg
	330 mg/mL solution	100 mg/mL
	182 mg/mL drops	50 mg/mL
Iron glycinate chelate (20 % of elementary iron)	150 mg Tablets	30 mg
	300 mg Tablets	60 mg
	500 mg chewable Tablets	100 mg
	250 mg/mL drops	50 mg/mL
Iron carbonyl (33 % of elementary iron)	400 mg Tablets	120 mg

Adapted from Zago MA, Falcão RP & Pasquini; Tratado de Hematologia, 2013 Atheneu.

Table 4 – Potential indications for parenteral iron replacement.

Intolerance and/or failure to respond to oral formulations
Concomitant use of erythropoiesis-stimulating agents
Post-bariatric surgery (and other conditions with absorptive limitations)
Inflammatory bowel disease
Pre-operative (especially <6 weeks before surgery)
Postoperative period
In order to avoid allogeneic transfusions in PBM programs
heart failure
Chronic renal failure and hemodialysis
Pregnancy (Second and third trimesters)

Adapted from Cappellini, Musallam KM, Taher (2020) [1]

intravenous iron formulations available in the country. It is important to remember that although serious reactions, such as anaphylactoid reactions, are rare (<1:200,000), the infusion must be carried out in a place with trained staff and adequate structure to deal with possible complications. It is recommended that the patient remains under observation for 30 min after the end of the infusion.[10]

The total replacement dose of iron can be calculated using the Ganzoni formula. Figure 2 shows an example of the calculation. For high dose formulations there are also simplified tables to determine the amount to be replaced (see Tables 6 and 7).

Preoperative use of erythropoietin

The use of recombinant erythropoietin (rEPO) is being recommended in the presence of preoperative anemia after excluding the possibility of nutritional deficiencies, hematological malignancies and autoimmune diseases.[6] rEPO can be used in preoperative treatment protocols for anemia of chronic disease, if there are no contraindications and always with parallel treatment of the underlying disease.[5] Elderly patients with chronic kidney disease or myelodysplastic syndrome usually respond well to EPO. It is important to ensure that iron stores

Table 5 – Characteristics of endovenous iron formulations.

	Saccharate ferric hydroxide	Ferric carboxymattose	Ferric derisomaltosis
Presentation (ampule)	100 mg/5 mL	500 mg/10 mL	500 mg/5 mL and 1000 mg/10 mL
Maximum dose per infusion	200 mg	20 mg/kg or 1000 mg	20 mg/kg
Dilution (solution)	0.9 % saline solution	Pure or 0.9 % saline solution	Pure or 0.9 % saline solution
Maximum dilution	1 mg of iron/mL	2 mg of iron/mL	25 mg/mL
Time of infusion	100 mg ≥15 min 200 mg ≥30 min	≥15 min	≥15 min
Necessity of test dose	No	No	No
Pediatric use*	Yes	No	No
Use during gestation**	Yes	Yes	Yes

Adapted from Auerbach M., Adamson JW.; How we diagnose and treat iron deficiency anemia; AJH; 2016 and Girelli D et al.; Modern iron replacement therapy; Clinical and pathophysiological insights; International Journal of Hematology 2018;107:16–30.

* Maximum dose of 3 mg of elementary iron/kg per dose. Do not exceed a total dose of 500 mg.
** Use from the second trimester of gestation.

Necessity of iron (mg of iron) = body weight* (Kg) x (Intended Hb – Real HB) x 2.4 + reserve iron* (500-1000 mg/Kg) Example: 49-year-old woman with 65 Kg, menorrhagia, oral iron intolerance, Current Hb: 7.5 g/dL, Ferritin: 3 mcg/L, preoperative of hysterectomy (Desired Hb: 13 g/dL) Calculation: (65 x (13-7.5) x 2.4) + 500 = 858 + 500 = 1358 mg of iron
Saccharate ferric hydroxide (100 mg/ampule) 14 ampules: 7 infusions of 200 mg (maximum 3 infusions per week or 600 mg/week)
Ferric derisomaltosis (500 mg and 1000 mg/ampule) Dose of 1500 mg (23 mg/Kg) – max 20 mg/Kg per infusion – Split in two infusions with an interval of one week
Ferric carboxymattose (500 mg/ampule) Dose 1500 mg (23 mg/Kg) – (max of 1000 mg/week or 20 mg/Kg per infusion) – Split in two infusions with an interval of one week

Figure 2 – Calculation of parenteral iron replacement.

*Use ideal body weight for obese and pre-gestational patients.

Girelli D et al.; Modern iron replacement therapy; Clinical and pathophysiological insights; International Journal of Hematology 2018;107:16–30.

Table 6 – Simplified table to calculate Ferric carboxymattose.

Hb (g/dL)	Body weight: 35–70 Kg	Body weight: >70 Kg
<10	1500 mg	2000 mg
≥ 10	1000 mg	1500 mg

Table 7 – Simplified table to calculate Ferric derisomaltosis.

Hb (g/dL)	Body weight: <50 Kg	Body weight: 50–70 Kg	Body weight: >70 Kg
<10	500 mg	1500 mg	2000 mg
≥ 10	500 mg	1000 mg	1500 mg

are adequate when starting EPO treatment. In this case, the use of intravenous iron should be preferred.[5] rEPO has been increasingly used in Patient Blood Management (PBM) protocols to preoperatively optimize erythrocyte mass and thus reduce the number of transfusions required. Experience, especially in major orthopedic surgeries, such as hip and knee arthroplasty, shows a significant improvement in hemoglobin and a reduction in the need for transfusions, without any increase in mortality or adverse events.[11] Good results are also being obtained in cardiac surgery, even with a short surgery interval, using a high dose of EPO in a small number of applications.[12]

The risks and benefits of EPO must always be contemplated and to do so, the underlying cause and severity of the anemia, individual characteristics of the patient, type of procedure and use of perioperative venous thromboprophylaxis must be considered. The biggest concern is the increased risk of thrombotic events, which has been observed with prolonged use of EPO targeting high hemoglobin levels (>13 g/dL) in patients with chronic kidney disease and oncological diseases.[13,14] Therefore, when defining an institutional PBM protocol, the use of rEPO should not be adopted as a universal measure to correct anemia in any patient or for any procedure; it is necessary to adopt evidence-based guidelines and also individualize the patient's risk.

Recommendations

We recommend that for the effective management of patients' anemia, the following actions be observed:

1. Early detection: Regular screening for anemia, especially in high-risk patients or those scheduled for elective surgery, is vital. This allows healthcare professionals to identify anemia at an early stage and implement appropriate interventions promptly.
2. Identifying underlying causes: It is essential to identify and address the underlying causes of anemia, which can range from nutritional deficiencies (e.g., iron, vitamin B12 and folate) to chronic illnesses and bleeding disorders.
3. Nutritional support: in cases of nutritional deficiencies, appropriate supplementation and dietary modifications should be prescribed to restore adequate levels of iron, vitamins or minerals.

4. Iron replacement: Iron deficiency anemia is one of the most common types of anemia. Oral or intravenous iron supplementation may be prescribed to replenish iron stores and increase hemoglobin levels.
5. Erythropoietin (EPO) therapy: In certain situations, particularly for patients unable to receive blood transfusions, erythropoietin-stimulating agents may be used to stimulate red blood cell production.
6. Preoperative optimization: If surgery is planned, sufficient time should be allowed for correction of anemia before the procedure. This may involve postponing elective surgeries, when possible, to give the patient enough time to respond to treatment.
7. Collaborative care: Effective management of anemia requires collaboration between different medical specialties, including surgeons, hematologists, and anesthesiologists. Each plays a crucial role in assessing and addressing a patient's anemic status and coordinating appropriate care.

Conclusion

By effectively managing anemia, especially before and after surgery, healthcare professionals can significantly improve patient outcomes, reduce surgical risks, and improve postoperative recovery. Early detection, addressing underlying causes and implementing necessary interventions are essential steps to ensure patients are in the best possible condition for surgery and can undergo the procedure with minimal complications.

Conflicts of interest

The authors declare no conflicts of interest.

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