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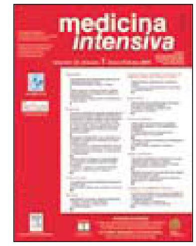

REVIEW

Anemia and transfusion therapy: an update

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Abstract
Anemia is one of the most prevalent diseases in the general population and is a very frequently found condition in medical and surgical patients in all medical specialties. A good evaluation of its clinical impact and its therapeutic possibilities is essential. Allogenic blood transfusion is a useful procedure in anemia management, although it has important adverse effects. It is the responsibility of the clinician to know and to take into account all the available alternatives for the treatment of anemia. Blood transfusions, erythropoiesis-stimulating agents, iron therapy (oral and endovenous) and other therapeutic alternatives must be rationally used, in accordance with the currently available clinical evidence. This review article summarizes some epidemiological characteristics of anemia, its clinical evaluation and the main therapeutic possibilities based on the present knowledge, placing special emphasis on the critically ill patient.

PALABRAS CLAVE
Anemia;
Transfusión;
Ferroterapia

Actualización en anemia y terapia transfusional

Resumen
La anemia representa una de las patologías más prevalentes en la población general y constituye una entidad extremadamente frecuente en pacientes médicos y quirúrgicos de todas las especialidades. Una correcta valoración de su impacto y de las posibilidades terapéuticas resulta crucial. La transfusión de sangre alogénica representa una medida eficaz en el manejo de la

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anemia, pero no está exenta de importantes complicaciones. Es responsabilidad del clínico conocer y sopesar todas las alternativas disponibles para el manejo global de la anemia. Transfusiones sanguíneas, agentes estimuladores de la eritropoyesis, ferroterapia (oral y endovenosa) y otras alternativas terapéuticas han de ser empleadas de forma racional y ajustándonos a la evidencia clínica disponible hasta la fecha. El presente artículo de revisión resume algunas características epidemiológicas de la anemia, su valoración clínica y las principales alternativas terapéuticas a la luz de los conocimientos actuales, con especial énfasis en el paciente crítico.

Introduction

General epidemiology of anemia

Anemia is one of the most common disorders or comorbidities, particularly in the elderly population (17-63%).[1,2] Anemia, defined by the World Health Organization (WHO) as hemoglobin (Hb) values of <13 g/dl in adult males and <12 g/dl in non-pregnant women, alters the efficacy of tissue oxygen supply and constitutes one of the main causes of complications and mortality, hospital admission and the prolongation of hospital stay, and impairment of patient quality of life.[1] Ferropenic anemia, regarded as the most prevalent disorder in the world, affects approximately 25-30% of the population.[3] Anemia due to chronic disease (ACD) is the most common form of anemia in hospitalized and critically ill patients, and accounts for one-third of all cases of anemia in elderly individuals.[1,3,4] Anemia associated to chronic renal failure (secondary to erythropoietin (EPO) deficiency, ACD, erythropoiesis inhibitors, nutritional deficiencies and uremic toxicity, among others) is highly prevalent, and is proportional to the degree of renal dysfunction.[2,5-7] Anemia in oncological patients (prevalence 14-77%) combines characteristics of ACD and of other types of anemia: ferropenic, megaloblastic, myelosuppressive and hemolytic.[8,9] Often underdiagnosed and under-treated, such anemia constitutes a negative prognostic factor, has an adverse effect upon patient quality of life, and can complicate the response to chemotherapy and radiotherapy.[10,11] Patients admitted to Critical Care show a high prevalence of anemia (40-70%), and have important transfusion needs - the underlying etiology being of a multifactorial nature.[12-16] Allogenic blood transfusion (ABT) is extremely useful for the treatment of anemia and is the only viable option in many patients. However, such transfusions constitute a limited resource (despite the 81 million units of blood donated each year, according to data from the WHO), and are not without important associated complications.[9,15-20]

General assessment of anemia

The general objectives of the treatment of anemia are to minimize the symptoms and systemic complications associated to hypoxia, and to improve patient quality of life and survival.[21] Under physiological conditions, O_2 distribution (proportional to cardiac output and blood O_2 content) is four times greater than the amount actually consumed- thus guaranteeing a sufficient supply to meet the tissue needs even under conditions of anemia ("physiological reservoir").[22-24] The *hypoxia inducible factor* molecular cascade, activated in response to hypoxia, coordinates a range of genes in charge of cell and tissue modifications destined to adapt to the situation of hypoxia.[25] The adaptive responses to anemia include central, regional, microcirculatory and cellular changes, with an increase in the tissue extraction of O_2.[15,21,22] Hemoglobin is usually used as an indicator of both erythrocyte mass and of O_2 release, though there are few data in humans defining a hemoglobin level below which oxygen release is compromised and tissue hypoxia manifests - at least in situations of chronic anemia.[26,27] Based on indirect parameters (arterial oxygen saturation, lactate levels), the transfusion trigger or threshold in normovolemic patients without cardiovascular disease is considered to be about 7 g/dl of hemoglobin.[4,13,15,16,18,21-23,27] The research study carried out by Quintana et al. (involving a questionnaire in 84 Spanish ICUs) confirms the fundamentally orientative usefulness of the hemoglobin values for deciding the use of ABT (ABT rate 20-40%), though there appears to be general agreement that transfusion is indicated when hemoglobin <7 g/dl (10 g/dl in the case of patients with heart disease).[28] In 1999, Hébert et al.[4] (TRICC study, a randomized clinical trial (RCT) involving 838 normovolemic critical patients) confirmed the equivalence, in terms of complications and mortality, of a restrictive transfusion strategy (transfusion trigger 7 g/dl, maintaining Hb levels of 7-9 g/dl) versus a more liberal strategy (transfusion trigger 10 g/dl, range 10-12 g/dl). Specifically, the restrictive strategy allowed a 54% reduction in the number of transfusions (2.6 vs 5.6 red cell concentrate units/patient).[13,15,18] The authors also observed a decrease in mortality after 30 days with the restrictive transfusion strategy in the subgroup of patients with an APACHE-II score of ≤ 20 (8.7% vs 16.1%) and in patients <55 years of age (5.7% vs 13%).[4] Critical patients with acute ischemic events and in the early phases of severe sepsis could represent important exceptions to the safety of a restrictive transfusion strategy (recommended trigger or threshold <8-10 g/dl).[16,29] On the other hand, the increase in hemoglobin and available O_2 is not always associated to a parallel increase in tissue oxygen consumption and to reversal of the deleterious effects of anemia.[20,23,26,27,30] The explanation of such a phenomenon may imply a series of factors (2,3-diphosphoglycerate depletion, stored red cell rigidity, mitochondrial dysfunction).[23] Recent studies question the validity of hemoglobin as a universal indicator for ABT - suggesting other tissue oxygenation and consumption parameters as possible physiological indicators for ABT (mixed venous saturation, intracerebral tissue O_2 pressure, oxygen extraction index (near-infrared spectroscopy), central nervous system processing latency period (P300 latency), gastric mucosal pH, etc.).[13,21,22,26,30] Despite its universal use, it has not been clearly demonstrated that ABT systematically improves tissue oxygenation or the prognosis of anemic patients.[23,27,29-31] The study of Leal-Noval et al. (prospective, with 60 anemic and stable neurological trauma patients) recorded an increase in brain tissue oxygenation (brain tissue oxygen partial pressure $P_{bt}O_2$) 6 hours after ABT (in 78% of the cases) that proved more frequent in patients with lesser $P_{bt}O_2$ baseline values.[32] Zygun et al. (RCT involving 30 patients with severe head injuries) confirmed an increase in $P_{bt}O_2$ (in 57% of the cases) proportional to the post-transfusion increase in hemoglobin that in turn was more pronounced in patients with a lactate / pyruvate index of >25, but with no effect upon brain metabolism.[33] To date, no studies provide firm support of the use of ABT in the treatment of anemia in hemodynamically stable critical patients without evidence of acute bleeding, and the available data confirm that hemoglobin values of 7-9 g/dl are well tolerated by critical patients without acute bleeding.[13,27,29] At present, the recommendation is to evaluate the use of ABT according to physiological parameters - the hemoglobin value alone not constituting an exclusive or sufficient criterion in this sense.[23,31] Napolitano et al. recently published a clinical guide on ABT especially oriented towards the critical and traumatologic patient setting.[27] The authors considered ABT to be clearly indicated in patients with evidence of hemorrhagic shock, and potentially indicated in cases of acute bleeding associated to hemodynamic instability or an insufficient availability of oxygen - recommending a restrictive transfusion strategy (Hb <7 g/dl) in stable anemia patients, with the possible exception of individuals with myocardial ischemia (level 1 recommendation). These investigators suggest linking hemoglobin to the patient hemodynamic status, the duration of anemia and other cardiopulmonary parameters as indicators for ABT (level 2 recommendation). Lastly, the guide contemplates a series of measures destined to reduce the need for ABT: the potential use of recombinant erythropoietin, a reduction of blood extractions (in number and volume), and the use of blood sample reinfusion devices and perioperative recovery.[27]

Epidemiology of anemia in the critical patient

Anemia in patients admitted to Intensive Care Units is highly prevalent (40-70%), and represents the most frequent laboratory test alteration.[16,20,34] In critical patients, anemia is of a multifactorial origin: ACD, perioperative bleeding, frequent laboratory test extractions, gastrointestinal bleeding, coagulopathy, extracorporeal techniques, nutritional and/or iron deficiencies, hemodilution, hemolysis, and drugs that interfere with erythropoiesis (e.g., angiotensin-converting enzyme inhibitors (ACEIs).[4,12,16,24,35] ACD is probably the most common etiology (up to 50% of all cases), and is defined as Hb <13 g/dl associated to an inflammatory process (clinical or biological evidence, such as C-reactive protein >1-5 mg/l), with ferritin >100 µg/l and transferrin saturation index (TSI) <16-20%.[16,34] Functional iron deficiency (FID), the substrate of ACD, is a consequence of iron retention within the biological deposits (macrophages of the reticuloendothelial system) and the inhibition of its intestinal absorption (degradation and downregulation of the ferroportin-1 intestinal transporter, upregulation of DMT-1, and an increase in ferritin) - thus reducing its availability for bone marrow erythropoiesis.[16,36,37] ACD is characterized by a coexisting inhibition of the proliferation of erythroid precursors and of the synthesis and bone marrow response to endogenous erythropoietin and stem cell factor.[36,37] Hepcidin hormone and other proinflammatory cytokines (TNFα, TNFγ, IL-1), actively synthesized in inflammatory, infectious, traumatologic and neoplastic processes, are regarded as the agents responsible for ACD.[16,34,36,37] FID is also responsible for immune response alteration in critical patients, contributing to a longer duration of the inflammatory response and patient stay, and a poorer prognosis.[34,38] The therapeutic possibilities in relation to anemia in the critical patient (analyzed more in detail below) can be grouped as follows: ABT; drug treatment (erythropoietic stimulators, iron therapy, antifibrinolytic / hemostatic agents); autologous blood donation and/or reinfusion programs; and restrictive and individualized transfusion criteria.[24]

Complications associated to ABT

ABT is a rapid and effective way to restore physiological hemoglobin values and thus increase the oxygen transport capacity. As such, it is particularly useful in the context of severe anemia and/or active bleeding, but is not without important complications: transmission of infectious diseases (due to the impossibility of viral detection, “window periods” or new emergent infections), risk of immune-type reactions (allergic, hemolytic, etc.), cardiopulmonary and thromboembolic complications, infections and other postoperative complications, prolongation of stay and increased hospital mortality, neoplastic recurrence, reversible posterior leukoencephalopathy, etc.[12,13,17-20,30,39-41] The potential complications and adverse effects of ABT must be weighed against the known increases in morbidity-mortality secondary to anemia.[23,42] Many studies have suggested an increase in patient mortality associated to ABT.[42] A number of multicenter observational studies have reported (evidence 2a) an association (dose-dependent) between ABT and increased morbidity-mortality in critical patients.[13,20,23] The ABC study (involving 146 European ICUs, N=3534 cases) revealed a prolongation of stay and an increase in percentage multiorgan dysfunction and mortality among patients administered ABT (mortality 23% vs 17%, p=0.002).[12] The CRIT study (involving 284 ICUs in the United States, N=4892 cases) in turn confirmed a prolongation of stay and an increase in mortality in critical care patients administered ABT (adjusted mortality risk 1.65, p<0.001).[31] However, other studies question the increase in mortality associated to ABT in critical patients, such as the SOAP study (involving 198 European ICUs, N=3147 cases), where multivariate analysis revealed no association between ABT and a poorer prognosis (RR 0.89, p=0.159).[42] The recent metaanalysis conducted by Marik et al.[15] (comprising 45 studies with s72,596 patients) confirms ABT as an independent predictor of mortality (OR 1.7), nosocomial infection and acute respiratory distress in patients at risk. Likewise, the retrospective study published by Khorana et al.[9] (multicenter, N=504,208 patients admitted to hospital due to neoplastic diseases) confirmed significant increments in the risk of developing venous and arterial thromboembolism, and of hospital mortality (OR 1.3) in patients administered ABT.

Infectious complications associated to ABT

The risk of blood transmission of pathogens has decreased drastically in the last decades thanks to the introduction of nucleic acid amplification techniques and other screening methods.[18,19,41,43,44] The microorganisms that potentially can be transmitted through ABT include viruses such as HBV (estimated risk 1:350,000), HCV (risk 1:1,800,000-10,880,000), HIV (risk 1:230,000-4,300,000), HAV, parvovirus B19, HLTV 1-2, CMV, EBV, West Nile virus, simian foamy virus, dengue virus, enterovirus coronavirus and prions;[19,41,43,45] bacteria such as *Treponema pallidum* and other genera (*Staphylococcus, Pseudomonas, Yersinia, Borrelia, Serratia* and *Enterobacter*); and protozoa (general *Leishmania, Trypanosoma, Plasmodium, Toxoplasma, Babesia*). The incidence of clinical sepsis secondary to ABT is estimated to be 1:250,000 transfusions, representing 14% of all deaths attributable to ABT in the United States.[41] Likewise, there is a persistent risk of blood transmission of still unknown viruses, viruses experiencing geographical expansion (chikungunya virus, St. Louis encephalitis virus, etc.), and of new variants of Creutzfeld-Jacob disease.[18,19,22,44]

Non-infectious complications associated to ABT

Non-infectious complications constitute the most frequent group of adverse effects following ABT.[41] Among the immune reactions, mention should be made of the following: hemolytic reactions, febrile reactions, allergic reactions, post-transfusional purpura, graft-versus-host reactions, alloimmunization, transfusion-related acute lung injury (TRALI) and transfusion-related immune modulation (TRIM).[41] Regarding the non-immune complications, mention should be made of transfusion error, iron overload, metabolic imbalances and transfusion-associated circulatory overload (TACO).[41] Error in administering the blood components heads the list of non-infectious complications associated to ABT.[46] The SHOT (Serious Hazards of Transfusion) report, in its 12th annual edition (2008), registered a 45% of events (477 cases) related to transfusion error, followed in decreasing order of frequency by acute allergic reactions (29%), anti-D immunoglobulin related events (13%) and hemolytic reactions (5%).[41,46] The transfusion error rate would be about 16.8 cases per 100,000 components, with an incompatible ABO classification transfusion rate of about 1:40,000.[43,46] Post-transfusion allergic reactions show an extremely variable prevalence (1-3% for urticariform presentations and 1:20,000-50,000 for anaphylactoid forms), with a broad range of associated signs and symptoms.[19,41,43,47] The rest of non-infectious mechanisms whereby ABT increases complications and mortality are varied, though mention should be made of transfusion-related acute lung injury (TRALI), transfusion-related immune modulation (TRIM), transfusion-associated circulatory overload (TACO) and microcirculatory alterations - though it is not always possible to individualize the concrete contribution made by each of them.[16,18,41,47] TRALI is a serious adverse effect of uncertain etiology is one of the main sources of post-transfusion iatrogenesis.[43,48] Frequently underdiagnosed, TRALI is presently regarded as the most common and serious complication associated to ABT, representing the main cause of ABT-related death in the United States, followed by hemolytic reactions and sepsis.[21,48] It is characterized by acute lung damage associated to bilateral, non-cardiogenic lung edema, hypoxemia, dyspnea, tachypnea, cyanosis, hypotension and fever.[16] TRALI appears in the first hours after ABT, and may be regarded as a particular form of acute respiratory distress syndrome.[43,48] Anti-HLA and anti-granulocyte antibodies, reactive lipids and cytokines from the donor (particularly female donors) targeted to recipient leukocytes have been proposed as etiological agents, stimulating the release of oxidases, inflammatory mediators and complement, altering the permeability and integrity of the pulmonary microcirculation, and triggering the TRALI effect.[19,43] Its estimated incidence is 1:4000-8000 transfusions, with an associated global mortality of 5-25%. The condition requires conservative management (oxygen, intravenous fluid therapy) and, occasionally, mechanical ventilation and other invasive maneuvers.[19,43] Transfusion-related immune modulation (TRIM) is characterized by an immunosuppressive state linked to ABT, which has been associated (observational studies) to an increased incidence of pneumonia, urinary infection, mediastinitis, sepsis, postoperative infection, the reactivation of latent viruses and, after oncological surgery, to an increase in tumor recurrence. The vasoactive substances released by the transfused leukocytes and lymphocytes could be responsible for this immune modulating effect, associated to downregulation of cellular immunity (dysfunction of natural killer (NK) cells, T cells and antigen-presenting cells (APCs), etc.) and upregulation of humoral immunity (IL-4, IL-5, IL-6, IL-10).[16,18,19] Although there are no conclusive data indicating a reduction in the rates of infection, complications, mortality or neoplastic recurrence with leukocyte depletion in ABT (with the exception of heart surgery, where a reduction in short-term mortality has been documented), universal leukocyte depletion (practically total elimination of leukocytes in allogenic blood components using specific filters) has been implemented in the European Union (since 2002 in Spain).[18,19,21,23,49] Prolonged storage of the red cell concentrate bags ("storage damage") may imply morphological (membrane alteration and loss of elasticity and deformation capacity) and functional deterioration (reduction of 2,3-diphosphoglycerate, nitric oxide (NO) and ATP) of the erythrocytes, with deleterious effects upon their half-life, oxygen affinity and capacity to favor vasoconstriction, endothelial damage, tissue ischemia and, presumably, infection.[15,18,23,43,50] A number of observational studies have evidenced an association between ABT stored for over 2-3 weeks and the appearance of postoperative complications, and a prolongation of hospital stay and/or increased short- and long-term mortality.[50] A variety of substances are present in high concentrations in the stored red cell bags (histamine, cationic eosinophilic protein, myeloperoxidase, lipids, etc.), and may act as immune regulators and contribute to the development of immune suppression, TRALI and tissue damage.[51] In turn, transfusion-associated circulatory overload (TACO) is secondary to an alteration in the alveolo-capillary hydrostatic pressure gradient as a consequence of volume overload, with an estimated incidence of 1-11%and involving a broad range of symptoms. Patients with cardiopulmonary disease or renal failure, and children, are particularly vulnerable to TACO.[16,41]

Alternatives to ABT

The recovery of hemoglobin levels by means other than ABT would contribute to clinical improvement of the patient and to a reduction in complications and mortality - in many cases avoiding unnecessary transfusions.[4,16-18,20,28] The administration of iron (via the oral or parenteral route) and the use of erythropoiesis stimulating agents (ESAs) are the two most widely used effective pharmacological alternatives to ABT.[5,16,52] Likewise, preoperative autologous donation programs and the use of antifibrinolytic and hemostatic agents have been able to effectively reduce the need for ABT in many surgical disciplines (in association to adjuvant ESAs and/or iron therapy).[53]

Erythropoiesis stimulating agents (ESAs)

Human erythropoietin (EPO) is a 165-amino acid polypeptide mainly synthesized by the peritubular cells of the renal interstitial compartment, in response to a drop in hematocrit, hypoxemia and/or increased oxygen affinity of hemoglobin. The genic expression of EPO is regulated by multiple transcription factors, including the hypoxia-inducible factor pathway, activated in response to hypoxia.[25,54] EPO is the principal bone marrow erythropoiesis regulating hormone.[3,55] Different types of recombinant exogenous EPO (rHuEPO), darbepoetin-alpha and methoxypolyethlyeneglycol-beta (CERA, or continuous erythropoietic receptor activator) constitute the main ESAs available on the market.[54] The administration of rHuEPO, introduced in the early 1990s, has clearly demonstrated its efficacy in the treatment of anemia in patients with nephrological, oncological, hematological or liver diseases, ACD, anemia associated to the treatment of AIDS, anemia of the premature infant, and in elective major orthopedic, cardiovascular, digestive and gynecological surgery (in the context of perioperative or autologous donation programs).[2,5,7,17,53,56-58] Following their administration (subcutaneous or intravenous), ESAs mimic the effects of endogenous EPO and stimulate erythropoiesis by inhibiting apoptosis of the erythroid precursors and promoting their proliferation and maturation.[5,17] The clinical response to such treatment (73-96%) manifests as an increase in reticulocyte counts within 3-10 days and a rise in erythrocyte counts within 1-2 weeks.[17] The intensity of the response depends on the ESA dose, the concomitant inflammatory and/or systemic disorders, and the availability of other substrates that are essential for erythropoiesis (iron, vitamin B_{12} and folic acid).[17] However, the use of these agents is expensive, and they are not without important complications (arterial hypertension, thromboembolism, hyperkalemia, headache, red cell aplasia, skin rash, influenza symptoms, the possibility of tumor progression and shortened survival in neoplastic patients (enrolled in ESA programs with hemoglobin targets of >12 g/dl), exacerbation of diabetic retinopathy, etc.) - treatment requiring careful adjustment of the administered doses.[14] In Spain 6 types of ESAs are currently available: epoetin-alpha, epoetin-beta, epoetin-delta, epoetin-zeta, darbepoetin-alpha and CERA, with differences in composition, receptor affinity and half-life.[5,7,54,57] Alternative forms of presentation of EPO are being investigated, such as the inhalatory and intramuscular routes.[54] New and complex modifications of the EPO molecule, gene therapy and fusion proteins, hypoxia-inducible factor stabilizers and mimetic substances (such as Hematide®) constitute future lines of research and treatment in erythropoietic stimulation.[5,7,54] Despite a qualitative and quantitative decrease in erythropoiesis in critical patients, the bone marrow is able to respond to the administration of ESAs.[16] However, the data available on the usefulness of ESAs in critical patients are contradictory.[7] The first RCTs on the use of ESAs in critical patients (Corwin et al. [2002], Silver et al. [2006]) revealed a significant decrease in transfusion needs in patients treated with ESAs - with no differences in terms of morbidity or mortality.[16,59,60] Recently, Corwin et al.,[14] in a multicenter clinical trial with 1460 critical patients, showed that the administration of epoetin-alpha (40,000 IU/week, associated to iron) did not reduce the transfusion needs or mortality, except in the subgroup of trauma patients that received ESA (adjusted mortality risk after 140 days of 0.4). The metaanalysis conducted by Zarychanski et al.[35] on the use of rHuEPO in 3326 critical patients (epoetin-alpha, mainly at a dose of 40,000 IU/week) evidenced a small reduction in the number of transfusions with respect to the control group (saving >0.5 units/patient), with no impact upon mortality, hospital stay, stay in the ICU or the need for mechanical ventilation. The authors therefore do not recommend the routine use of ESAs in critical patients. Possibly careful patient selection and the fundamented use of the coadjuvant treatments might optimize treatment with ESAs in critical patients (still without technical indication).[16] The EORTC (European Organization for Research and Treatment of Cancer) and SEOM (Spanish Society of Clinical Oncology) guides on the use of ESAs in anemia in neoplastic patients confirm their efficacy in increasing the hemoglobin levels, reducing the need for transfusions (by up to 50%) and improving patient quality of life, though without consistent data confirming improvement in patient survival, local tumor control, time to disease progression or disease-free interval.[52] On the other hand, several recent studies and reviews (BEST, ENHANCE, Amgen 2000-0161 trials) have evidenced a significant increase in venous thromboembolism, locoregional tumor progression and cardiovascular mortality in patients with different neoplasms subjected to ESA therapy with a hemoglobin target of ≥12 g/dl. As a result, different healthcare authorities recommend caution with the use of these agents and advise hemoglobin monitorization to precisely adjust the ESA dose in order to be able to avoid the need for ABT.[52,57,58] The recommendations (year 2007) of the American Society of Clinical Oncology (ASCO) and the American Society of Hematology (ASH) on ESA use in oncological patients with anemia associated to chemotherapy include starting treatment with subcutaneous ESAs in the event of hemoglobin values of ≤ 10 g/dl, with monitorization of the iron deposits and the administration of iron supplements - a value of 12 g/dl being established as the hemoglobin target concentration.[8] All these scientific societies disadvise ESA use in anemic neoplastic patients without concomitant chemotherapy.[8] Similarly, Several

Table 1 Oral iron formulations available in Spain

Compound	Type of iron	Elemental iron content
Ferrous sulfate	Iron (II)	80 mg/pill
Ferrous lactate	Iron (II)	37.5 mg/vial
Ferrous gluconate	Iron (II)	25 or 80 mg/tablet
Ferrous glycine sulfate	Iron (II)	100 mg/capsule
Ferrocholinate	Iron (III)	112.6 mg/vial or 56.3 mg/ sachet
Protein succinylate	Iron (III)	40 mg/vial
Ferrimannitol	Iron (III)	20 mg/vial or 40 mg/sachet

studies (CHOIR, CREATE) have evidenced a rise in cardiovascular complications and global mortality among patients with chronic renal failure subjected to ESA therapy with a hemoglobin target of >12 g/dl.[5,7] The Committee for Human Medicinal Products (CHMP) of the European Medicines Evaluation Agency (EMEA) recommends ESA use for the management of symptomatic anemia in nephrological and neoplastic patients for reaching and maintaining a maximum hemoglobin concentration of 12 g/dl.[57]

Oral iron therapy

The administration of oral iron supplements is the least invasive method for restoring the body iron deposits.[17] The different iron salts available on the market (table 1) show minimal differences in terms of their absorption (10-15%), and contain variable amounts of mineral iron. The main disadvantage of oral iron supplementing is the high incidence of associated gastrointestinal side effects (10-40% of cases, in the form of abdominal pain, heartburn, nausea / vomiting, constipation or diarrhea) - with treatment non-compliance rates of over 10-20%[61-63] The efficacy of such treatment depends on the degree of absorption, which in turn is conditioned by the amount, posology, condition of the biological deposits, erythropoietic activity and intraluminal factors that interfere with absorption of the product.[3] The oral absorption of iron is often unable to compensate for continuous losses.[63] Due to the effect of hepcidin hormone (a key regulator of iron metabolism), intestinal absorption and mobilization of the iron deposits from the macrophages of the reticuloendothelial system are intensely inhibited in the presence of ACD - thus justifying the inefficacy of oral iron therapy in such situations and the need to often resort to alternative administration routes (parenteral iron), associated or not to ESAs.[3,6,63] Treatment with oral iron (2-3 mg/kg/day or 50-400 mg/day) increases the hemoglobin levels starting from the first to second week of therapy, with normalization within 1-4 months. It is necessary to prolong treatment for several months (3-6 months) in order to fill the biological deposits. In contrast, intravenous iron allows faster bone marrow response and filling of the deposits (1-2 weeks).[63]

Parenteral iron

Since 1998, parenteral iron administration has become a key element in the treatment of patients with chronic renal failure enrolled in renal replacement programs.[6] Compared with oral iron therapy, the association of ESAs and intravenous iron is superior in terms of the correction of anemia or renal, neoplastic, ACD and perioperative origin, and makes it possible to delay and reduce the ESA dose required (by up to 30-70%).[6,7,17] This synergic interdependence is based on the requirement of adequate iron deposits for maintaining the transferrin saturation needed for erythropoiesis hyper-stimulated by ESA treatment. Its optimum safety profile (with a prevalence of serious adverse effects of 2.2-5 cases per million doses) and contrasted efficacy define the current parenteral iron formulations as an option with an enormous potential in transfusion medicine - representing an extremely useful alternative to ABT.[17,62] Globally, intravenous iron is more effective, predictable, better tolerated and is able to more quickly improve patient quality of life, compared with oral iron supplementing.[7] Functional iron deficiency (FID), characteristic of ACD, responds satisfactorily to parenteral iron administration.[63] A number of parenteral iron formulations are available on the market (table 2), with differences in terms of their physicochemical characteristics and dosing regimens. Some presentations allow high-dose intravenous iron dosing (200-1000 mg/dose) or monodose administration (total dose infusion), thus simplifying the posology (reduction of the number of doses and stay) and accelerating restoration of the iron deposits and erythropoiesis.[62,63] At present, the indications for intravenous iron are taken to be the following: intolerance, non-compliance, inefficacy or impossibility of oral iron therapy, malabsorptive disorders or inflammatory bowel disease, FID, and the need for immediate iron replacement for effective erythropoiesis (perioperative anemia, concomitant ESA therapy, autologous donation programs, anemia associated to neoplasms and chemotherapy, patients receiving renal replacement therapy, and anemia associated to pregnancy or puerperium).[6,56,62,63] Critical patients present FID that proves difficult to correct with oral iron therapy. Inadequate erythropoiesis and the immune alterations associated to FID can benefit from the administration of parenteral iron, thus contributing to lessen the transfusion needs and potentially also to shorten patient stay, as well as reducing the inflammatory parameters and patient morbidity and mortality (although the risk / benefit ratio has not been clearly established).[16] The study published by Van Iperen et al. evidenced a tendency towards lessened transfusion needs, inflammatory response and mortality in critical patients with anemia administered intravenous iron saccharose (alone or combined with ESAs).[64] Georgopoulos

Table 2 Parenteral iron formulations

Molecule	Brand name	Drug company
Iron dextran, high MW	Dexferrum®	American Regent Laboratories, Inc.
Iron dextran, low MW	INFeD®	Watson Pharma, Inc.
	Cosmofer®	Pharmacosmos A/S
Iron gluconate	Ferrlecit®	Watson Pharma, Inc.
Iron saccharose	Venofer®	Vifor Int./Grupo J. Uriach, S.A.
	Feriv®	GES Genéricos Españoles
	Normon®	Laboratorios Normon, S.A.
Iron carboxymaltose	Ferinject®	Vifor Int.
	Injectafer®	American Regent Laboratories, Inc.

et al. recorded a decrease in the percentage of transfusions (and in the number of concentrate units used) in a group of critical patients, as a result of the administration of intravenous iron associated to ESAs (ESA dose-dependent efficacy), though with no impact upon the stay in Intensive Care or on patient mortality.[65] The review published by Muñoz et al. proposes a dose of 50 mg/day (100 mg/day in the case of bleeding patients and/or individuals stimulated with ESA therapy) in order to cover the erythropoietic requirements in critical patients.[16]

Other alternatives

Advances in the knowledge of the physiopathology of anemia due to chronic disease (ACD) have made it possible to develop new treatment modalities.[17] The use of antagonists of hepcidin or inflammatory mediators, as well as of hormones and cytokines that stimulate erythropoiesis, represent possible and interesting future strategies for the management of anemia.[3,54] In the surgical setting, and apart from autologous donation programs and cell saver systems, we have antifibrinolytic and hemostatic agents for managing perioperative bleeding and reducing the need for transfusions, such as aprotinin, desmopressin, ε-aminocaproic acid and tranexamic acid, with demonstrated efficacy in heart, digestive and orthopedic surgery, among others.[17,18,24] Aprotinin exerts antifibrinolytic action based on the inhibition of key enzymes involved in fibrinolysis and the inflammatory cascade.[17,66] Despite demonstration of its efficacy in heart surgery and other surgical specialties, its marketing has been suspended as a result of a multicenter RCT that evidenced an increase in mortality among heart surgery patients who received aprotinin.[67] Desmopressin, an antidiuretic hormone analog, exerts its hemostatic effect by increasing both the plasma concentrations of factor VIII and Von Willebrand factor and platelet adhesion.[17] Its possible benefit in critical patients has not been established.[24] In turn, ε-aminocaproic acid and tranexamic acid exert antifibrinolytic action by inhibiting both plasmin and plasminogen activation (tranexamic acid offers longer action and is 6-10 times more potent), with demonstrated efficacy in reducing blood losses and the need for transfusions in surgical settings.[17,68] The CRASH-2 study (a multicenter RCT), currently ongoing, will assess the effect of tranexamic acid in trauma patients with or at risk of suffering significant bleeding, in terms of mortality and transfusion requirements.[24]

Lastly, artificial oxygen transporter solutions (fluorocarbonate emulsions and artificial hemoglobin solutions) constitute promising lines of research in blood replacement therapy, though the promising initial results have been moderated by recent studies that have raised doubts as to their safety, adverse effects and clinical efficacy.[17,18,47,69]

Conclusions

Anemia is extremely frequent in patients in all disciplines (particularly critically ill individuals), and requires a multidisciplinary approach and a rational and individualized use of the available therapeutic resources. Allogenic blood transfusion (ABT) is a rapid and effective option for correcting anemia, but it is not without important complications and controversies. ABT must be indicated on an individualized basis depending on a series of physiological parameters - not only on the existence of low hemoglobin concentrations. The use of pharmacological alternatives (ESAs, iron therapy and antifibrinolytic / hemostatic agents), the reduction of laboratory tests (in number and volume), autologous donation programs and blood reinfusion protocols, and the adoption of restrictive transfusion strategies, can offer a significant reduction in blood transfusion demand and contribute to a more rational, safe and efficient use of ABT.

Conflict of interest

The authors declare no conflict of interest.

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