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Review article

Anaemia, iron, transfusion and therapeutic alternatives. A review from a surgical perspective

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ARTICLE INFORMATION

ABSTRACT

Anemia is very common entity or comorbidity in surgical patients. Its management involves a multidisciplinary approach with the aim of optimizing the available therapeutic resources with individualized care for each clinical situation. Rational use of blood transfusions, iron therapy (oral and intravenous), erythropoiesis stimulating agents and other therapeutic alternatives by physicians must achieve maximal benefit with minimal complications for our patients. This review article summarizes the main characteristics of anemia, iron metabolism, erythropoiesis and therapeutic alternatives from a surgical perspective in the light of present knowledge

Anemia, hierro, transfusión y alternativas terapéuticas. Revisión desde una perspectiva quirúrgica

RESUMEN

La anemia representa una entidad o comorbilidad extremadamente frecuente dentro de la población de pacientes quirúrgicos. Su manejo implica un abordaje multidisciplinar con el fin de optimizar los recursos terapéuticos disponibles de forma individualizada en cada situación clínica. El uso racional por parte del clínico de transfusiones sanguíneas, ferro-terapia (oral y endovenosa), agentes estimuladores de la eritropoyesis y otras alternativas terapéuticas ha de proporcionar el máximo beneficio a nuestros pacientes con las mínimas complicaciones posibles. El presente artículo de revisión resume las principales caracterís-ticas de la anemia, metabolismo férrico, eritropoyesis y alternativas terapéuticas desde una perspectiva quirúrgica, a la luz de los conocimientos actuales.

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General epidemiology of anaemia

Anaemia is one of the most prevalent human pathologies, especially in elderly people (17%-63%), and occurs very frequently (prevalence of 40%) in medical and surgical patients.[1-6] Anaemia, defined by the WHO (1968) as haemoglobin levels <13 g/dl in men and <12 g/dl in non-gestating women, alters the efficacy of transporting oxygen to tissues and constitutes one of the main causes of complications and mortality, need for hospitalisation and increased duration of hospital stays, and reduced quality of life.[2-4,5,7-11] This symptom/comorbidity is associated with a variety of pathologies, and is often caused by multiple factors.[7,12] By analysing all of the causes of anaemia in patients over the age of 65 years, one third have a ferropoenic origin, one third occur due to chronic inflammatory processes, and the final third have an unknown aetiology.[1,4,5,13-16] Anaemia of chronic disease (ACD) is the most common type of anaemia in hospitalised and critical patients.[17] Anaemia in cancer patients, which is extremely frequent (up to 44%-77%), combines characteristics of ACD and other types of anaemia (ferropenic, megaloblastic, myelosuppressive, haemolytic, etc.).[12,18-22] Patients admitted to intensive care units also have a high prevalence of anaemia and transfusion requirements (40%-60%).[23-29]

Iron metabolism, erythropoiesis, and abnormalities

Due to its ability to accept and donate electrons, iron is an essential element in many biological functions, such as oxygen transport (the haem group in haemoglobin), energy production, enzyme activity, DNA synthesis and haematopoiesis, immune response, and other processes.[30-34] Its ability to produce toxic oxygen free radicals forces the organism to regulate iron levels precisely.[31,35] The total body content of iron is estimated at 35-50 mg/kg (3-4 g in total), and the daily intake requirement is 1 mg/d (2-3 mg/d in women

of reproductive age).[36-38] Iron metabolism represents a very complex and highly regulated cycle (Figure).[37] The normal diet in Spain implies a daily intake of 10-30 mg of iron.[26,38] Non-haem iron from the diet (85%-95% of the total) is absorbed in the proximal portion of the duodenum through a transmembrane transporter (DMT-1) in the apical border of enterocytes.[14,30,31,34,39] Haem iron acquired through dietary intake (derived from the haemoglobin and myoglobin in animal source foods) is incorporated into the organism through mechanisms that have not yet been clarified.[30,40] Within the enterocyte, a small fraction of the absorbed iron is stored (bound to ferritin) and the rest crosses the basolateral membrane through the ferroportin 1 transporter, in order to achieve circulation and bind with transferrin.[7,14,30,31,34,41] Transferrin is a β_1-globulin synthesised by hepatocytes, and its primary function is to bind itself to trivalent iron, keep it soluble, and distribute it to the bodily tissues.[14,38,42,43] Transferrin-bound iron (3-4 mg) is replaced or exchanged 10-15 times per day and, is, therefore, the most important dynamic pool for erythropoiesis. The erythroid precursors in the bone marrow require 20-30 mg of iron per day for the mitochondrial synthesis of the haem group in haemoglobin and to form new erythrocytes.[37,43] These cells take up iron through endocytosis of the transferrin-iron complexes in the plasma through cellular transferrin receptors (TfR1).[34,36,37,42] Erythropoiesis also requires the stimulation of renal erythropoietin (EPO) and other cytokines and cofactors.[7,14,37,38] The velocity at which iron can be transported is one of the principle limiting factors in erythropoiesis in the bone marrow. Senescent erythrocytes are phagocytised by macrophages of the spleen, liver, and bone marrow (reticuloendothelial system, RES) 120 days after their incorporation into the bloodstream.[38] Haemoglobin is hydrolysed in the cytoplasm of the macrophage, the haem group is catabolised, and iron is released, which is stored bound to ferritin, and to a lesser degree, as haemosiderine.[38,44] Ferritin, the main protein used to store iron intracellularly, is a reserve for the synthesis of compounds that require iron, a system for storing the iron in a soluble, non-toxic form, and a known acute-phase reactant.[37,45-48] Cells release
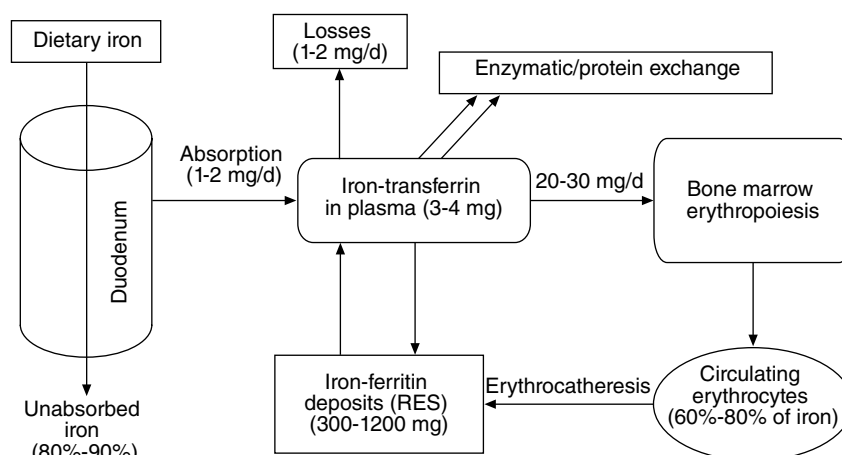

Figure 1 – Iron metabolism. RES indicates reticuloendothelial system.

Table 1 – Characteristics of ferropenic anaemia and ACD			
Variable	Ferropenic anaemia	ACD	Mixed anaemia
Iron	Reduced	Reduced	Reduced
Transferrin	Increased	Normal or reduced	Normal or reduced
TSI	Reduced	Normal or reduced	Reduced
Ferritin	Reduced	Increased or normal	Normal or reduced
sTfR	Increased	Normal	Increased or normal
sTfR/log ferritin	High (>2)	Low (<1)	High (>2)
Cytokines and CRP	Normal	Increased	Increased
ACD indicates anaemia of chronic disease; sTfR, soluble transferrin receptors; TSI, transferrin saturation index.			

a small quantity of ferritin into circulation, in proportion to the content of biological deposits.[14] From these biological deposits, iron can be incorporated into plasma transferrin, which transports it to the bone marrow and other tissues again.[7,38,43] This recirculation circuit constitutes the main source of iron for erythropoiesis (99%), given that iron absorbed by the intestine generally only compensates for the small daily losses (1-2 mg/d) due to small haemorrhages, cell desquamation, and losses through sweat, urine, and faeces.[43,45] In the body, iron in the plasma (bound to transferrin) and iron in biological deposits (bound to ferritin) are kept in dynamic equilibirum.[7] Inflammatory processes (acute and chronic) and other pathological situations alter this balance, playing a central role in the development of anaemia.[49] According to the most recent research, hepcidin, a hormone synthesised in the liver, plays a key role in regulating iron metabolism.[14,31,39,43,44,46,50] Its synthesis responds to erythropoietic demand, the concentration of transferrin, iron deposits, hypoxia, and infectious inflammatory states (IL-6 levels, lipopolysaccharides, etc.) and exerts a systemic and coordinated control on intestinal absorption and iron recycling and storage.[14,31,39,43,51-53] Hepcidin appears to exert a double inhibitory effect on macrophage ferroportin-1 (inhibition of iron release) and on DMT-1 in the enterocyte (inhibiting intestinal absorption of iron).[50,54,55] The net result of this activity is reduced intestinal iron absorption and the inhibition of iron release into the plasma from biological deposits, thus diminishing the quantity of iron available for erythropoiesis.[14,39,41,43,49,55,56] In this way, the interaction between hepcidin and ferroportin maintains the extracellular concentrations of iron at stable levels (6-27 µmol/l in the plasma).[43] The synthesis of hepcidin increases when the body is in a state of iron overload and decreases with anaemia, hypoxia, and iron deficiency, thus maintaining homeostasis.[38] Iron deficiency anaemia (IDA) or ferropenic anaemia develops when the organism does not have enough iron to be incorporated into erythroid precursors, due to a depletion of the deposits from haemorrhage (acute or chronic), malnutrition/malabsorption, or increased iron demand (gestation, infancy). This is characterised by haemoglobin <13 g/dl (in men), a transferrin saturation index (TSI) <16%-20%, ferritin <30-100 µg/l, an increase in soluble transferrin receptors (sTfR), and a high sTfR/log ferritin ratio (>2), in patients with no clinical or biochemical evidence of inflammation, and tends to be microcytic and hypochromic (Table 1).[2,13,14,46,57] ACD is the most common type of anaemia in hospitalised and critical patients, and can be defined as anaemia associated with inflammatory processes (with clinical or biological evidence, such as CRP >1-5 mg/l), with ferritin levels >100 µg/l, TSI <16%-20%, a normal concentration of sTfR, and a low sTfR/log ferritin ratio (<1), normally normocytic and normochromic (Table 1).[57-59] In ACD, the deficit of "available" iron, or functional iron deficiency (FID) is a consequence of the retention of iron in biological deposits (though downregulation of the ferroportin-1 transporter and upregulation of TfR1 and ferritin) and the inhibition of intestinal iron absorption.[37,46,59,60] Furthermore, the proliferation and differentiation of erythroid precursors is inhibited, along with a reduction in erythrocyte half-life, inhibition of the iron-transferrin bond, reduced synthesis and marrow response to endogenous erythropoietin, and increased phagocytosis of erythrocytes.[18,26,58,59] The molecules responsible for FID, especially hepcidin and a wide variety of cytokines and proinflammatory molecules (IL-1, IL-6, TNF-alpha, IFN-gamma, etc.) are actively synthesised during inflammatory and infectious processes (acute and chronic), systemic inflammatory responses (sepsis, trauma, multi-organ failure, or surgical aggression), autoimmune disease, and neoplastic diseases.[2,13,14,27,28,36,49,51,56,60-63]

Anaemia in surgery: prevalence and aetiopathogenesis

Anaemia is a condition/comorbidity that is very common among surgical patients, and normally arises from multifactorial causes. In general, 5%-80% of surgical patients suffer preoperative anaemia: one of the main reasons for allogeneic blood transfusions (ABT)[1,7,8,13,27,63-67] Patients are constantly operated on at greater ages and in more extreme conditions. Perioperative anaemia has, therefore, become a very frequent condition, whether due to digestive losses or chronic inflammatory processes, the underlying pathology of the patient (especially in neoplastic diseases), the surgical technique used (gastrectomy, gastric bypass, etc.), vitamin deficiency and malnutrition, the myelosuppressive effects of chemotherapy, perioperative blood loss, or due

to the systemic inflammatory response triggered by the surgical aggression.[2,61,62,68,69] In addition to perioperative haemorrhage, hyposideraemia and reduced transferrin and TSI levels are frequent during the postoperative period, with increases in ferritin levels.[51,70,71] This scenario implies a marked reduction in the availability and absorption of iron during the first 2-6 weeks following surgery, which hinders erythropoiesis and frequently leads to postoperative anaemia.[70-74] This situation often cannot be rectified by administering oral iron therapy, but does so with parenteral iron. This indicates altered patterns of iron release from the RES similar to ACD.[70,71] Therefore, postoperative anaemia (the same as anaemia in critical and septic patients) can be considered as an acute and transitory variation of ACD.[70] Several different studies have corroborated on the association between perioperative anaemia and increased incidence of complications, postoperative mortality, duration of hospital stay, and worsening of various parameters for quality of life.[27,66,75-85] Lastly, according to some studies performed on neoplastic patients, postoperative anaemia is a negative prognostic factor in terms of disease-free interval and survival.[86] The presence of chronic inflammatory processes and ferropenia constitute the primary aetiological factors of anaemia in surgical patients (64% and 23%-33% of all preoperative anaemias, respectively).[27,87] FID, the underlying mechanism in ACD, is present in many seriously ill and surgical patients, which increases hospitalisation time and mortality.[7,17,28,62,88] Dunne et al confirmed the presence of pre- and postoperative anaemia in 33.9% and 84.1% of cases, respectively, in a prospective study including 6301 patients that underwent elective, non-cardiac surgery; both circumstances (and ABT) were associated with increased mortality, postoperative pneumonia, and hospitalisation time.[75] Approximately 15%-23% of patients with solid tumours require ABT at some point during the progression of their disease.[89-91] Representative of this relationship, the incidence of anaemia susceptible to perioperative transfusions in patients with colorectal cancer (CRC) ranges between 20% and 85%.[13,92,93] In addition, postoperative anaemia constitutes one of the main complications in patients that undergo gastrectomy (20%-62%), and has a multifactorial origin: deficient vitamin B_{12} absorption due to the lack of intrinsic factor and disbacteriosis, folic acid deficiency, deficiency in the consumption and absorption of iron due to achlorhydria, etc.[64,69,94-101] Bariatric surgery is another facet of medicine that is intimately related to the development of mid- and long-term postoperative anaemia, with a prevalence of 16%–36% one year after surgery.[102-106] Vitamin deficiencies in these patients (vitamin B_{12} and folate) tend to be easily remediated through administering supplements.[104,106-108] However, iron deficiency (multifactorial) tends not to respond to oral iron therapy, occasionally requiring parenterally administered iron or even ABT.[103,104,107,108]

Anaemia in surgery: therapeutic possibilities

Due to both its frequency and clinical repercussions, anaemia represents an important problem in the

management of surgical patients, and so we often have to resort to ABT: a quick and efficient method of restoring haemoglobin values and avoiding the deleterious effects of severe anaemia.[27,59] On the other hand, ABT is an expensive and rare resource that is associated with several different known complications and adverse side effects that must be considered when prescribing it. The aetiology of the disease, the intensity of symptoms, associated comorbidity, and possible treatment alternatives should be taken into consideration.[109,110] In the specific case of digestive neoplasia, ABT has been associated with significant increases in postoperative infection rates, hospital stay duration and costs, neoplastic recurrence, and mortality.[28,64,65,109-117] The study by Sitges-Sierra et al (with 2809 colorectal resections) confirmed ABT as the most relevant risk factor in the development of postoperative infections.[109] Furthermore, Rovera et al, in a 110 patient study, confirmed that perioperative ABT was an independent variable for the development of infections of the surgical wound following oesophagectomy in the treatment of neoplastic disease.[111] Several studies performed in intensive care units have confirmed the association between ABT and duration of hospital stay and mortality.[7] These important adverse effects have led to the search for alternatives to ABT, such as administering iron (oral or parenteral), erythropoiesis-stimulating agents, or ESA [recombinant human erythropoietin (rHuEPO) and others], autologous transfusion, antifibrinolytics, controlled hypotension and intraoperative temperature, artificial oxygen carriers, and, obviously, a proper preoperative examination of the patient and a swift and clean surgical technique.[28,118-125] Furthermore, based on the study by Hébert et al (that demonstrated the effectiveness of a restrictive transfusional strategy as opposed to a more liberal approach), more restrictive criteria for transfusions are being used in surgical and critical patients (with transfusional thresholds around 7 g/dl and haemoglobin levels maintained at 7-9 g/dl, in the absence of organ failure), relegating the use of ABT to acute situations in haemodynamically compromised patients.[1,7,58,88,118,121,122,126-131]

Erythropoiesis stimulating agents in surgery

The administration of rHuEPO is a safe and efficient treatment for reducing the need for ABT during elective surgery in patients with preoperative anaemia that are candidates for procedures with major haemorrhagic losses.[89,92,119,132-134] Several different preoperative regimens have been used for subcutaneous administrations of ESA, from 300-600 UI/kg/week (3-4 weeks before the intervention) to 300 UI/kg/day (for 7-10 days before and 4-7 days after the procedure).[125,131,135,136] Several different studies have demonstrated a significant increase in haemoglobin values and a reduced need for ABT in patients that undergo surgery for gastrointestinal neoplasia and receive preoperative treatment of iron and rHuEPO at low dosages (including autologous transfusion programmes).[92,135,137-139] Levine et al showed that administering rHuEPO (250 UI/kg 3 times per week, along

with orally administered iron) during neoadjuvant treatment for rectal cancer significantly increased haemoglobin values and reduced the need for transfusions (0.4 vs 3.7 units per patient).[140] Qvist et al observed an increase in pre- and postoperative haemoglobin values and a reduced need for perioperative ABT in anaemic patients with CRC through perioperative administration of rHuEPO (300 UI/kg 4 days before the procedure and 150 UI/kg the following week) and preoperative oral iron therapy (200 mg/day for 4 days).[139] Christodoulakis et al demonstrated the efficacy of preoperative rHuEPO, oral iron therapy, and folic acid in increasing haemoglobin and haematocrit levels and reducing the need for transfusions in a randomised clinical trial (RCT) with 223 anaemic patients with CRC.[92] The preoperative administration of rHuEPO has been shown to be effective in elective urological cancer surgery and neoplasia of the head and neck.[141,142] Lastly, the postoperative administration of rHuEPO has been shown to reduce the need for ABT in patients with gastric neoplasia.[143] In 1994, the use of rHuEPO was approved in the EU as a coadjuvant in preoperative autologous donation programmes, and its efficacy has been confirmed in trauma patients, cardiovascular surgery, and patients with gastrointestinal (gastric, hepatic, and colorectal), gynaecological, and sacral neoplasia.[137,144-150]

Oral iron therapy in surgery

Oral iron therapy has demonstrated its efficacy in correcting anaemia and reducing the need for transfusion in scheduled digestive surgeries. Table 2 summarises the various types of oral iron administrations available, with minimal differences between them in terms of efficacy. In general, the recovery of haemoglobin levels starts 7-10 days after starting treatment. Okuyama et al showed that patients with CRC and anaemia that received preoperative oral iron therapy (200 mg/d for 2 weeks) required fewer intraoperative transfusions (9.4% vs 27.4%).[151] A recent RCT (with 49 cases) on patients waiting for scheduled colorectal surgery showed a significant reduction in the need for transfusions (26% vs 59%) with the preoperative oral administration of iron, constituting a simple and cheap method for avoiding ABT.[13]

Intravenous iron in surgery

The administration of intravenous iron represents an efficient and safe method for improving haemoglobin levels in surgical patients (Table 3). Several different studies have agreed on the efficacy of intravenous iron for accelerating the recovery of haemoglobin levels and reducing the need for perioperative ABT in general surgery, traumatology and orthopaedics, gynaecology and obstetrics, and gastroenterology, with significant improvements in rates of postoperative complications and infections, duration of hospital stay, and short-term mortality.[1,8,27,28,61,62,88,152-157] Some institutions in Spain use standardised protocols for the preoperative administration of intravenous iron in patients with digestive neoplasia.[28] The intravenous use of iron (whether associated or not to ESA) is of special interest in the treatment of anaemia in candidate patients for surgery scheduled within a short period of time.[1,7,62,135,138,158] Intravenous iron is able to correct FID and haematological parameters, reduce the rate of ABT, and improve the immunological situation of surgical patients, and so it should be used both in preoperative preparation and postoperative correction of anaemia.[28]

Planned autologous transfusion in surgery

The techniques for planned autologous transfusion consist in collecting, storing, and later reinfusing the patient's own blood. In general, there are five different types available: predeposited autologous whole blood transfusion/

Table 2 – Oral iron preparations available in Spain

Compound	Type of iron	Elemental iron content
Ferrous sulphate	Iron (II)	80 mg/tablet
Ferrous lactate	Iron (II)	37.5 mg/vial
Ferrous gluconate	Iron (II)	25 or 80 mg/pill
Ferrous glycine sulphate	Iron (II)	100 mg/capsule
Ferrocholinate	Iron (III)	112.6 mg/vial or 56.3 mg/packet
Iron protein succinylate	Iron (III)	40 mg/vial
Ferri-mannitol	Iron (III)	20 mg/vial or 40 mg/sachet

Table 3 – Preparations of parenteral iron

Molecule	Commercial name	Laboratory
High-molecular weight iron dextran	Dexferrum®	American Regent Laboratories Inc.
High-molecular weight iron dextran	INFeD®	Watson Pharma Inc.
	Cosmofer®	Pharmacosmos A/S
Iron gluconate	Ferrlecit®	Watson Pharma Inc.
Iron sucrose	Venofer®	Vifor Int./Grupo J.Uriach S.A.
	Feriv®	GES Genéricos Españoles
	Normon®	Laboratorios Normon S.A.
Ferric carboxymaltose	Ferinject®	Vifor Int.
	Injectafer®	American Regent Laboratories Inc.

donation, preoperative autologous erythroapheresis, acute normovolemic haemodilution, intraoperative blood salvage (through cell savers), and postoperative blood salvage (from postoperative drains).[119,124,125,131,137,159] Autologous donation has shown to significantly reduce (31%-63%) the number of patients transfused during elective orthopaedic, cardiac, vascular, and oncological (tumours of the oesophagus, stomach, colon, etc.) surgeries.[131,160-165]

Antifibrinolytic substances in surgery

Aprotinin, desmopressin, ε-aminocaproic acid, tranexamic acid, and activated factor VII are the main antifibrinolytic substances currently available on the market.[166-169] The antifibrinolytic effect of aprotinin is based on the inhibition of key enzymes for fibrinolysis and the inflammatory cascade.[119] Several RCT and meta-analyses have shown the efficacy of this drug in heart surgery, in terms of reduced perioperative haemorrhage and conserved haemoderivatives, and several different studies confirm its usefulness in major orthopaedic surgery and elective liver surgery.[89,170-172] The commercial use of this medication was recently suspended due to a multi-centre RCT (the BART trial) that provided evidence of increased mortality in patients that underwent heart surgery while receiving aprotinin.[173,174] Desmopressin is a synthetic analogue of the antidiuretic hormone with haemostatic properties. Desmopressin has proven its efficacy in the prophylaxis of perioperative haemorrhage in patients with haemophilia, some forms of von Willebrand disease, platelet disorders, liver disease, and uraemia.[119,169] A similar antifibrinolytic action is provided by ε-aminocaproic acid by inhibiting both plasmin and the activation of plasminogen. Tranexamic acid has a similar antifibrinolytic activity, but with a more prolonged action and is 6-10 times more powerful. Both drugs have demonstrated their efficacy in reducing blood losses, transfusion needs, wound complications, and the number of reoperations required due to bleeding in general, digestive, cardiac, gynaecological, orthopaedic, and neurological surgery.[89,119,169,171,175-177] Recombinant activated factor VII brings about the production of large quantities of thrombin and fibrin, and is highly indicated in haemorrhagic episodes in haemophilic patients, congenital factor VII deficiency, Glanzmann's thrombasthenia, acquired coagulation disorders, severe multiple traumas, intracraneal haemorrhage, and as a prophylaxis in surgeries with a high risk of haemorrhage.[119,167,169,171]

Prohaemostatic materials and other measures in surgery

A wide variety of topically applied prohaemostatic materials are available on the market: bsorbable gelatine sponges or film, oxidised cellulose, microfibrillar collagen, topical thrombin, fibrin sealants, and platelet gels.[178] Intraoperative hypothermia is responsible for severe clotting abnormalities and platelet dysfunction. It is, therefore, crucial to maintain a normal body temperature during the surgical procedure. Lastly, artificial oxygen carriers, which are solutions that replace the intravascular volume with the ability to bind oxygen, represent one of the most innovative therapeutic fields in blood substitution.[119,123,179] Fluorocarbon emulsions and artificial haemoglobin solutions are the 2 major groups of substances that have been studied in clinical practice until now.[120,180] Intravenous liquid perflubron (Oxygent™, Alliance Pharmaceutical Corp.) is a fluorocarbonated that has been developed to temporarily increase oxygen delivery in patients with a risk of developing tissue hypoxia from acute anaemia (trauma or major surgery).[119] Its efficacy has been proven through a significant reduction in the need for ABT in patients scheduled for major surgery.[181] Artificial haemoglobin solutions (HBOC-201 Hemopure®, MP4 Hemospam® and others) have in some studies a high capacity for O_2 transport and reductions in the need for transfusions in some studies. These have been successfully used in phase I-III clinical trials in cardiac, vascular, and major orthopaedic surgeries, and in patients with ischaemic crises due to haemolytic anaemia. However, recent studies have raised doubts as to the safety and adverse effects of these products.[120,180,182-184] The research generated by these novel substances could, while not completely substituting blood transfusions, achieve a significant reduction in demand for transfusions and contribute to a more rational and efficient use of ABT.[185]

Conflict of interest

The authors affirm that they have no conflict of interest.

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