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Introduction

Blood-loss anemia is frequent in the perioperative setting and red blood cell transfusions are considered standard therapy for rapidly and effectively correcting hemoglobin concentration, both intra-operatively and postoperatively. Indeed, blood transfusions have become remarkably safer in the past 35 years, as developments for screening blood supplies have led to the successful response to both new and old health risks that threaten the safety of blood transfusion. Furthermore, recent developments in biotechnology have helped accelerate efforts to reduce serious hazards of transfusion. However, residual dangers of allogeneic blood products - including transfusion-transmitted diseases, alloimmunization, immunosuppression, [1-5] and more recently scarcity of banked blood - have prompted the development of alternatives to allogeneic blood transfusions. Although preoperative autologous blood donation has been in use since the 1990s and effective in reducing allogeneic transfusions, this approach still involves the risk of bacterial contamination, overstorage, and mismatch. In addition, the cost inherent to wastage is prohibitive in many countries. [6] Consequently, other alternatives such as erythropoietin (EPO) and iron therapy have recently received more scrutiny in order to develop cost-effective, safe blood sparing strategies.

1. Potential Roles for Iron Therapy

As far back as the early 1930s, an expanded understanding of erythropoiesis and the central triad of iron, erythropoietin, and committed erythroid progenitors highlighted the need for preventive and therapeutic iron supplementation in numerous contexts. [7, 8] Blood loss mechanisms and the relationship between erythropoietin, iron, and the erythropoietic response to anemia have been elucidated through clinical experience with preoperative autologous blood donations. A review article by Goodnough et al. summarizes the knowledge gained as a model of blood-loss anemia, namely repeated phlebotomy, in terms of the relationship between iron, erythropoietin, and erythropoiesis. [9]

In 1982, Finch and Huebers [8] identified a state of "relative iron-deficiency" (now commonly referred to as functional iron deficiency), in which increased needs for erythropoiesis exceed iron availability, even with replete iron stores. This assertion was based on a number of observations made in healthy subjects, patients with hereditary anemias, and patients with hemochromatosis. Most interestingly, patients with hemochromatosis (i.e. pathologic iron overload) undergoing serial phlebotomy can provide enough iron to increase their erythropoietic response up to 8 times greater than basal rates, while healthy subjects were shown to have difficulty providing sufficient iron to support erythropoiesis beyond three times the basal rate. [10, 11] This difference is attributed to the high serum iron concentration and transferrin saturation (TSAT) in patients with hemochromatosis. Since then, repeated phlebotomies for preoperative autologous donations have established the basis for an "experimental" model of blood-loss anemia and have confirmed the concept of iron-restricted erythropoiesis. [12]

In the late 1980s, the introduction of recombinant human erythropoietin (rHuEPO) led to a revitalized interest in iron therapy. The standard use of exogenous erythropoietin ultimately led to a greater understanding of iron metabolism and to confirmation of iron-restricted erythropoiesis. [12, 13] Indeed, aggressive autologous phlebotomy substantially increases endogenous erythropoietin response. However, in this state, no relationship exists between basal iron stores and increased erythropoiesis, suggesting adequate serum iron and TSAT. When exogenous erythropoietin is administered to further expand the erythropoietic response, iron-restricted erythropoiesis occurs. Moreover, serum ferritin and TSAT may decrease by 50% with erythropoietin therapy, despite an 8-fold increase in gastrointestinal iron absorption. [12]

1.1. Early Detection and Treatment of Functional Iron Deficiency

Traditional parameters that are indispensable to an anemia work-up include hemoglobin concentration, reticulocyte count, and RBC indices (mean corpuscular volume and mean corpuscular hemoglobin concentration. However, the early detection and treatment of functional iron deficiencies is also of critical importance, especially in order to ensure optimal results of erythropoietin therapy. [14] During repeated phlebotomy, there is little change in serum iron concentration until iron stores are exhausted. When iron stores are depleted, serum transferrin concentrations increase linearly and transferrin iron binding capacity reaches approximately 400 µg/dL, while TSAT falls below 15%. At this stage of iron deficiency, erythropoiesis becomes iron-restricted. [15] However, in patients receiving erythropoietin therapy, TSAT falls even when iron stores are replete. [16]

Reticulocytes are normally released from the marrow 18 to 36 hours before their complete maturation into erythrocytes, thus providing a real-time indication of erythropoiesis function. However, in the early phases of stimulated erythropoiesis, changes in absolute reticulocyte count reflect the release of immature reticulocytes from the marrow, rather than the true expansion of erythropoiesis. [9] Indeed, parameters such as low reticulocytes hemoglobin content (CHr) and percentage of hypochromic red blood cells (%HRC) are more accurate to assess functional iron deficiency. Therefore serum ferritin < 200 µg/L, TSAT < 20%, increase in % HRC, and low CHr values have been proposed as the most indicative parameters for the assessment of functional iron deficiency, outside the context of chronic renal function (CRF). [17]

1.2. The Basis for Perioperative Iron Therapy Strategies

Oral iron supplementation has been shown to be effective during endogenous erythropoietin mediated RBC expansion in contexts without active blood loss where there is no underlying condition or abnormality interfering with iron absorption or utilization. However, oral iron supplementation is usually insufficient in patients with ongoing blood loss. In this setting, large doses of oral iron (approximately 200 mg/day) are necessary to induce an optimal response, but with a potential risk of gastrointestinal intolerance that can lead to compliance problems. Additionally, in patients receiving erythropoietin therapy, oral iron may be insufficient to prevent iron-restricted erythropoiesis, [9, 14] particularly when iron stores are normal and iron absorption is consequently decreased. [18]

1.3. The Role of Intravenous Iron Supplementation

In patients with ongoing blood loss, intravenous iron supplementation usually becomes necessary to adequately support enhanced erythropoiesis. [19, 20] Intravenous iron alone has been shown to enable up to a 5-fold increase in erythropoiesis response to significant blood loss anemia in healthy subjects. [21, 22] In patients participating in a preoperative autologous blood donation program with erythropoietin therapy, a dose-response relationship exists between erythropoietin and RBC expansion. [23] However, by the second week of erythropoietin therapy, there is a decline in reticulocyte count that is accompanied by hypochromic RBC, indicating functional iron deficiency. [24] Such cases represent the main indications for intravenous iron supplementation. [14]

2. The Role of Intravenous Iron Therapy in Postoperative Anemia

Studies have shown that both major and minor surgery induce a state of iron deficiency that is compatible with a transient state comparable to anemia of chronic disease. During this state, iron stores in the reticuloendothelial system macrophages are normal. However, due to increased hepcidin synthesis iron is unavailable for erythropoiesis as a result of an alteration in the release of iron from macrophages and incorporation to transferrin. Biesma, et al. [25] demonstrated that blood loss is not essential to induce changes in iron status following surgery. In fact, studies show that functional iron deficiency can be caused by a postoperative systemic inflammatory response, in which mediators, such as interleukin-6, C-reactive protein, and tumor necrosis factor, are released following surgery. [26] Changes in C-reactive protein and variables of iron metabolism suggest a prolonged inflammatory effect from surgery. Moreover, the extent of iron deficiency is related to the extent of surgery. Studies also show that oral iron supplementation in the presence of normal iron stores are unable to correct functional iron deficiency. It is possible that decreased intestinal iron absorption - which is governed by iron reserves - associated with the inflammatory response, contribute to the inactivity of oral iron supplementation for the correction of anemia following surgery. Consequently, intravenous iron therapy has emerged as an option for the treatment of functional iron deficiency in postoperative patients.

2.1. Iron-Restricted Erythropoiesis and Iron Therapy

Aggressive autologous blood donation program - a model for blood loss anemia - leads to an estimated three-fold increase in erythropoiesis, through the action of endogenous erythropoietin. Studies indicate that oral iron supplementation is sufficient for expansion of RBC through endogenous erythropoietin. However, during erythropoietin therapy administered to increased the number of pre-deposit blood units, oral iron supplementation may be insufficient to prevent iron-restricted erythropoiesis. [9,] In fact, a study by Mercuriali found that patients receiving erythropoietin therapy and oral iron failed to maintain their reticulocyte response. In these circumstances, it appears that erythropoietin therapy had exhausted iron stores faster than oral iron could replace them. Conversely, patients receiving erythropoietin therapy and intravenous iron achieved the highest sustained reticulocyte response and the greatest volume of donated autologous blood. [27] Based on this understanding of iron-restricted erythropoiesis, intravenous iron therapy has emerged as a method to reduce postoperative anemia and iron deficiency.

2.2. Postoperative Benefits of Intravenous Iron Therapy

2.2.1. IV Iron Therapy and Ongoing Blood Loss or Refusal of Transfusion

Intravenous iron therapy can be beneficial in patients with ongoing blood loss or in patients who refuse transfusion because of religious reasons. Mays et al. [20] described a number of situations in which intravenous iron-dextran therapy was successful in the treatment of anemia that occurred in surgical or obstetric-gynecologic patients. Patients in the surgical group included those with normal or stable postoperative blood volume with unacceptably low hemoglobin, or iron-deficient patients with low hematocrit readings who were unable to receive blood for an elective surgery because of autoagglutinins or religious beliefs. The obstetric-gynecologic group included patients with menorrhagia and prepartum or postpartum anemia. Patients received a total dose infusion of iron-dextran (the dosage being calculated of each individual on the basis of patient's body weight, the most recent hemoglobin concentration and target hemoglobin concentration).

Main results:

- The average increase in hemoglobin concentration one week after iron-dextran infusion was 1.9 gm/dL. Some of the patients showed much greater increase.
- Mean corpuscular hemoglobin, mean corpuscular volume and means corpuscular hemoglobin concentration improved or were corrected within three weeks after intravenous iron therapy.
- The authors found that the response to intravenous iron was particularly impressive in patients with low serum iron and no chronic infection or cancer.
- Furthermore, hemoglobin and hematocrit increased significantly in several patients who had anemia, despite oral iron therapy and normal serum iron concentrations.

Even though these preliminary results were promising, it seems that the risk of anaphylactic shock (0.6 to 2.3%) associated with iron dextran was sufficient to preclude intravenous iron therapy from becoming first-line treatment to manage perisurgical anemia. Since the report of these findings in 1976, safer intravenous iron preparations such as iron gluconate and iron sucrose have been considered in the perioperative period.

2.2.2. IV Iron Therapy with or Without EPO Therapy in Post-Partum Anemia

Traditionally, postpartum anemia has been treated with iron or blood transfusion. However, the risks associated with allogeneic blood transfusion have relegated this practice to a last resort intervention in young or otherwise healthy mothers. In its place, rHuEPO plus intravenous iron sucrose has been proposed as a treatment alternative. Breyman et al. [28] compared the effects of intravenous and oral iron therapy (100 mg intravenous iron sucrose once, followed by oral iron therapy during 6 weeks) alone or in combination with rHuEPO. The study demonstrated that a single dose of rHuEPO and iron therapy stimulated erythropoiesis, even in patients in which erythropoietin levels were high after acute peripartal hemorrhage. Results of the study also suggest that inflammatory cytokines, released after spontaneous or operative deliveries, might negatively influence endogenous erythropoietin levels.

In a subsequent study, Brayman et al. [29] compared the effects of (1) rHuEPO plus IV iron sucrose, (2) rHuEPO placebo plus IV iron sucrose, (3) and oral iron sulfate alone, to treat postpartum anemia. In this study, hematocrit increases were greater after administering rHuEPO plus IV iron, compared to administering iron alone (IV or oral). In addition, the study found that oral iron supplementation was insufficient for adequate erythropoiesis in this patient population.

Since these pilot studies, other trials - mainly performed to evaluate the efficacy and safety of iron sucrose - have shown that when anemia occurs in the postpartum period, storage iron is usually either low or depleted. Intravenous iron supplementation is effective and safe in replenishing iron reserves and supplying appropriate amounts of iron for anemia correction. Intravenous iron therapy appears to have a beneficial effect in decreasing the number of patients who require blood transfusion in the postpartum period. In a subset of patients in whom erythropoietin production is blunted because of the inflammatory response to delivery (with or without surgical intervention), rHuEPO can further increase hemoglobin production. Adjuvant treatment with rHuEPO and intravenous iron may also be of benefit in other situations where a more rapid restoration of the red blood cell mass is required. The concomitant use of intravenous iron is recommended in such settings in order to prevent or overcome functional iron deficiency.

For details on iron therapy during postpartum anemia, please refer to the relevant chapter: Management of Iron-Deficiency Anemia in Pregnancy and the Postpartum.

2.2.3. IV Iron Therapy and Total Hip Replacement or Hip Fracture Repair

Unilateral total hip replacement results in a substantial blood loss that leads to transfusion of allogeneic blood in 30-70% of these patients. To reduce allogeneic blood transfusion requirements in this context, intravenous iron has been successfully used to accelerate recovery of hemoglobin levels.

To determine the effect of preoperative intravenous iron on blood transfusion requirements, Munoz et al conducted a study of 24 patients who received 300 mg of IV iron sucrose prior to undergoing surgery for total hip replacement. The control group consisted of a retrospective series of 22 patients who did not receive iron prior to undergoing this surgery. [30]

Main results:

- In the group receiving intravenous iron, there was a reduction in the transfusion index for patients with a preoperative hemoglobin < 13 g/dL, but not for patients with a preoperative hemoglobin > 13 g/dL; however, patients with the higher preoperative hemoglobin had a shorter length of hospital stay.
- There was also a trend toward a lower postoperative infection rate in the group receiving intravenous iron, but there was no statistically significant difference in postoperative infection rate between the treatment and control groups.

In total hip replacement patients, administration of iron sucrose appears to (1) reduce requirements of allogeneic blood transfusion, (2) potentially reduce the risk of postoperative infection, and (3) shorten length of hospital stays.

2.2.4. IV Iron Therapy in Post-Hemodilution Anemia in Pediatric Cardiac Surgery

The main complication following hemodilution in pediatric cardiac surgery is anemia. To evaluate the efficacy and safety of a single dose of intravenous iron sucrose (5mg/kg) to treat anemia, Hulin and Durandy [31] conducted an open randomized study of 93 patients (age, 6 months to 12 years) weighing less than 20 kg and undergoing cardiac surgery with extracorporeal circulation.

Main results:

- When compared to the control group (n = 44, no iron supplementation), the group receiving intravenous iron therapy (n = 44) had a higher ferritin concentration (215 ±87 versus 101 ±55 µg/L; $P < 0.001$).
- Reticulocyte rate at postoperative day 5 was also higher in the IV iron sucrose group (3.25 ±1.16% versus 2.65 ±0.97%; $P < 0.005$).

A single dose of intravenous iron is associated with improved erythropoiesis in hemodilution-induced anemia in pediatric patients undergoing open-heart surgery.

2.2.5. IV Iron Therapy Following Spinal Surgery

During spinal fusion surgery, massive bleeding often leads to anemia in the postoperative period. Two groups of 16 infant and adolescent patients were treated with either intravenous iron sucrose complex or oral iron fumarate. [32] The efficacy of iron therapy was compared by evaluating hemoglobin levels in the postoperative period, following anterior and/or posterior spinal fusion.

Main results:

- Hemoglobin levels increased by 0.25 g/dL in the group receiving oral iron fumarate and 0.36 g/dL in the

group receiving intravenous iron sucrose ($p = 0.003$).
- Treatment duration was 5-6 days in the iron sucrose group, compared to 2-3 months needed in the oral iron group.

Intravenous iron therapy complex has greater efficacy than oral iron therapy for the restoration of postoperative hemoglobin levels after spinal surgery in children.

3. The Role of Preoperative Intravenous Iron Therapy

3.1. Transfusion Requirements

The requirement for blood transfusion during surgery depends on the initial RBC mass - reflected by hemoglobin concentration - on the day before surgery, the volume of perioperative blood loss, and the lowest hemoglobin concentration that the patient can tolerate (transfusion trigger). The volume of blood loss depends on (1) the type of surgery, (2) the quality of surgical hemostasis, and (3) the surgical and anesthetic technique. [33] Lowering the transfusion trigger is dependent on the patient's physiologic conditions. The volume of blood loss that the patient can tolerate before reaching the hemoglobin threshold can be modulated by optimizing the patient's initial RBC mass. This can be achieved through rHuEPO therapy and/or intravenous iron therapy. Algorithms should be developed to optimize the benefit/cost ratio by identifying patient populations likely to benefit from preoperative rHuEPO therapy. [34]

3.2. Clinical Evidence of Benefits From Intravenous Iron Therapy

3.2.1. Iron Deficiency Restricts Erythropoiesis and Anemia Correction

Iron deficiency is a limiting factor for stimulating erythropoiesis and correcting anemia. Therefore, replete iron stores and iron availability must be assured in the perioperative period. In this context, studies have demonstrated that rHuEPO has greater efficacy to correct preoperative anemia or stimulate preoperative hemoglobin synthesis, when combined with intravenous iron therapy, rather than oral iron therapy. Rohling et al. [35] examined the effects of three weeks treatment with rHuEPO (200 units/kg), in combination with either intravenous iron sucrose (200 mg twice weekly) or oral iron sulfate (160 mg/day) was compared in 12 patients, preparing for elective surgery with expected blood loss > 500 mL.

Main results:

- Serial reticulocyte counts increased in both groups, but were higher after day 15 in the IV iron + rHuEPO group compared to the oral iron + rHuEPO group (35% versus 18.6%, respectively; $p < 0.01$).
- Although hemoglobin levels increased in both treatment groups, there was no significant intergroup differences; however, IV iron sucrose steepened this increase in hemoglobin level as documented by a significant intragroup increase at various time points.
- Intravenous iron sucrose also prevented iatrogenic iron depletion as demonstrated by ferritin levels (266.8 ±144.3 µg/L in IV iron compared to 34.0 ±47.6 µg/L in the oral iron group; $p < 0.01$), three days before surgery.

Preoperative intravenous iron therapy significantly boosts the hematopoietic response to rHuEPO in healthy subjects undergoing elective surgery. Whereas oral iron therapy fails to maintain adequate iron stores and only weakly stimulates erythropoiesis, intravenous iron therapy steepens the increase in hemoglobin while preventing iatrogenic iron depletion.

3.2.2. Intravenous Iron Therapy Stimulates Erythropoiesis in Patients With Hip Fracture

Elderly patients undergoing surgery for hip fracture repair are transfused to avoid the risk of postoperative anemia. However, risks of allogeneic blood transfusion, including postoperative infection have prompted the review of this transfusion practice and stimulated the search for alternatives. A blood saving protocol using intravenous iron therapy combined with rHuEPO has been successful in accelerating the recovery of hemoglobin levels in these patients. Garcia-Erce et al. [36] conducted a prospective observational study to evaluate the effect of a blood-saving protocol (BSP group) on transfusion requirements and postoperative morbidity and mortality in patients with hip fracture (n = 83). The BSP consisted of perioperative iron sucrose (3 x 200 mg/48 hours) in all patients plus rHuEPO (1 x 40, 000 IU SC) in those with admission hemoglobin levels < 13 g/dL; a parallel series of 41 patients with hip fracture within the same hospital served as the control group.

Main results:

- The proportion of patients who received perioperative or postoperative allogeneic blood transfusions was significantly lower in the BSP group compared to controls: 71% vs. 24%, ($p < 0.001$) and 19.3% vs. 53.7% ($p < 0.01$), respectively.
- The number of units of allogeneic blood transfused perioperatively was also significantly lower in the BSP group compared to controls (median 0, range 0-4, versus median 2, range, 0-4; $p < 0.001$).
- In the BSP group, the reticulocyte count ($p < 0.001$), serum ferritin ($p = 0.043$) and soluble transferrin receptor concentrations ($p < 0.001$) were significantly higher at postoperative day 7, and RBC distribution width was wider, compared to controls.
- In addition, the rate of postoperative infections was significantly reduced in the BSP group versus controls (12.5%

versus 31.5%; p = 0.016).

A protocol consisting in administering IV iron sucrose alone or combined to rHuEPO in selected patients seems to reduce transfusion needs in patients undergoing hip fracture repair and is associated will lower infectious complications.

Conclusion

Several clinical settings have provided natural experiments to further our understanding of the relationship between erythropoietin, iron, and the erythropoietin response to anemia. Under normal conditions in healthy subjects, plasma iron turnover is not significantly affected across a broad range of low and high TSAT. However, observations of patients with hemochromatosis have demonstrated an erythropoietin response that is up to eight times greater than basal rates, whereas healthy persons have difficulty providing sufficient iron to support rates of erythropoiesis greater than three times basal rates. When increased erythron requirements exceed the available supply of iron, even in the presence of storage iron, a state of functional iron deficiency develops, causing iron-restricted erythropoiesis. Such cases represent the main indications for intravenous iron therapy.

Functional iron deficiency is frequent and neglected in the perioperative setting. Serum ferritin < 200 µg/L, TSAT < 20%, increase in %HRC, and low CHr values have been proposed as the most indicative parameters for the assessment of functional iron deficiency outside the context of CRF. The early detection and treatment of functional iron deficiency is essential, particularly for optimal results with erythropoietin therapy. Although more trials are needed, data supports the benefit of intravenous iron therapy in several contexts (Table 1).

Experience with the use of intravenous iron therapy is extensive. In fact, intravenous iron therapy has been used internationally, in clinical settings, for more than 60 years. In a number of studies, intravenous iron therapy was shown to be clearly superior to oral iron therapy. Although effective, iron dextran has been associated with rare but life-threatening allergic reactions, whereas other intravenous iron preparations have been associated with significantly less serious hypersensitivity reactions. Currently, intravenous iron sucrose is considered the safest IV iron preparation.

In the late 1980s, the introduction of rHuEPO led to a revitalized interest in the use of iron therapy, either in combination with rHuEPO therapy, or alone. Intravenous iron therapy can be used in a variety of clinical settings, as long as iron parameters are carefully monitored. With increased availability of intravenous iron preparations and current data supporting the efficacy and safety of intravenous iron therapy in general and iron sucrose in particular in reducing transfusion requirements and postoperative morbidity, it is essential to conduct more trials on intravenous iron therapy alone or in combination with rHuEPO in the perioperative setting.

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