



Intravenous Iron in Cardiac Surgery

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In patients presenting for elective cardiac surgery, preoperative anemia is associated with increased risk of postoperative transfusion, morbidity, and mortality. Intravenous iron therapy, with or without erythropoietin (EPO), may play an important role in the correction of preoperative anemia, as well as in facilitating autologous blood donation, thus reducing the risk of patient exposure to allogeneic blood transfusions. In addition, postoperative intravenous iron may act by treating decreased iron availability, thus increasing the action of both endogenous and exogenous EPO and improving the quality of postoperative recovery. As a short-term therapy, intravenous iron does not put the patient at risk for long-term iatrogenic effects.

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Cardiac surgery, with or without cardiopulmonary bypass (CPB), results in a significant blood loss that predisposes the patient to perioperative allogeneic blood transfusions, which may result in increased postoperative morbidity.¹ If patients at high risk for requiring perioperative transfusions (eg, anemic patients) can be identified in the preoperative period, prophylactic and therapeutic modalities can be targeted to those patients who might benefit from such treatments.

Moreover, preoperative anemia has been associated not only with an increased risk of allogeneic transfusion,² but also with a greater risk for lower survival after coronary artery bypass grafting.³ Disease severity and comorbidity have the greatest effect on mortality in anemic patients, which may be aggravated by transfusion of stored blood, anemia being just a consequence of some other disorders such as acute or chronic blood loss, nutritional iron deficiency, renal failure, malignancy, or chronic inflammatory disease. Consequently, the first step to be taken in the setting of elective cardiac surgery will be the preoperative identification and evaluation of anemia early enough to implement the appropriate treatment. Whenever possible, preoperative pharmacologic treatment of anemia should be used, rather than transfusion.⁴

Postoperative anemia may occur in up to 90% of patients, most probably due to perioperative blood loss and blunted

erythropoietic response. It is well known that major surgery is followed by a systemic inflammatory response whose humoral mediators (eg, interleukin [IL]-1, interferon- γ , and tumor necrosis factor- α) inhibit erythropoiesis both directly by suppressing erythroid colony growth and indirectly by suppressing erythropoietin (EPO) production. These inflammatory cytokines also induce a status of decreased iron availability, ie, a clinical situation where the iron stores in the bone marrow macrophages is normal but this iron is not available for erythropoiesis, due to an alteration of its release from the macrophages. Also, intestinal iron absorption is inhibited, due to a reduction of its release through the enterocytic basolateral membrane. Hepcidin, a hepatic acute-phase protein, seems to play a major role in both alterations.⁵

Intravenous iron emerges as a timely therapeutic option for the treatment of decreased iron availability in these patients, since once injected in vivo the iron-carbohydrate complexes are metabolized, the iron is released and binds to transferrin in the plasma, and the redundant carbohydrate moiety is then cleared via the liver. Hence, intravenous iron therapy, with or without EPO, may play an important role in perioperative anemia management in order to decrease the need for allogeneic blood transfusions and improve patient outcomes.

Perioperative Treatment With Iron and Erythropoietin

Recently, we performed a study of the prevalence of anemia and alteration of iron metabolism in a series of 60 consecutive patients undergoing cardiac surgery. There were 30 myocardial revascularizations without CPB, and 16 valve prostheses and 14 mixed surgeries with CPB. Preoperatively, 27 (45%)

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patients were anemic, 13 (22%) had serum iron less than 50 $\mu\text{g/dL}$, 25 (42%) ferritin less than 100 $\mu\text{g/L}$, 17 (28%) transferrin saturation less than 20%, 13 (22%) C-reactive protein greater than 1 mg/dL, and 10 (17%) IL-6 greater than 10 pg/mL.⁶ In addition, patients treated with angiotensin-converting enzyme (ACE) inhibitors had lower hemoglobin (Hb) levels, erythropoietin concentrations, and reticulocyte indices, and a higher incidence of anemia.⁷ Thus, chronic administration of ACE inhibitors to patients with coronary artery disease or cardiac valve pathology seems to be associated with a higher incidence of preoperative anemia, most probably due to a reduced EPO synthesis. These data suggest that anemic patients scheduled for cardiac surgery might benefit from treatment with iron and EPO.

In adult patients scheduled for cardiac surgery, perioperative treatment with EPO reduced the risk of exposure to allogeneic blood transfusion (60/195, 31% v 56/104, 54%) (relative risk [RR], 0.57; 95% confidence interval [CI], 0.43 to 0.75; $P < .001$), but there was a great variability in total EPO dose and iron supplementation, as well as in outcomes (Table 1). EPO plus oral iron resulted in either a reduction of the percentage of transfused patients and the number of transfused units,^{8,9} or had no significant effect¹⁰ (Table 1). In pediatric cardiac surgery, perioperative administration of EPO plus intravenous iron resulted in a reduction of both the percentage of transfused patients and the number of transfused units.¹¹ Overall, the use of intravenous iron seems to allow for a reduction in the total dose of EPO (Table 1).

Preoperative Autologous Blood Donation

Preoperative autologous blood donation (PABD) before elective cardiac surgery has proved to be an effective measure to reduce the exposure of patients to allogeneic blood transfusion. However, in patients who are unable to compensate the Hb drop due to repeated phlebotomy, the subsequent reduction in oxygen delivery to the myocardium may aggravate myocardial ischemia.

In a small trial ($n = 32$), anemic adult patients (Hb < 11 g/dL) who received EPO (3×500 IU/kg subcutaneously) and oral iron (plus intravenous iron, in hospitalized patients,

if ferritin < 100 $\mu\text{g/L}$) donated 2 to 3 blood units, and only 25% received allogeneic transfusions. In contrast, patients in the control group who received oral iron only were not able to donate blood and 100% received allogeneic transfusions ($P < .05$).¹² Similar data have been reported for the use of EPO to facilitate PABD in a series of children ($n = 78$) undergoing open-heart surgery (Table 2).¹³ Overall, the administration of iron, with or without EPO, to anemic patients scheduled for cardiac surgery allowed them to enter the PABD program and reduced the exposure to allogeneic blood transfusions (RR, 0.17; 95% CI, 0.09 to 0.16; $P < .001$).

The combined results of seven clinical trials (318 patients) showed that, for patients included in a PABD program, EPO administration facilitates collection of the required units and prevents a preoperative Hb drop. In addition, exposure to allogeneic transfusion was less likely among patients who received EPO than among those who did not (RR, 0.40; 95% CI, 0.26 to 0.60; $P < .001$) (Table 2).^{8,14-19} There were no differences in either the allogeneic transfusion rate or the total EPO dose administered between patients receiving oral iron and those receiving intravenous iron (Table 2).

Postoperative Anemia

In the postoperative period, several studies have evaluated the effectiveness of oral²⁰ or intravenous iron replacement therapy²¹⁻²³ for treatment of acute anemia after cardiac surgery. The administration of oral iron after uncomplicated coronary artery bypass surgery did not help to restore red blood cell mass nor to maintain total body iron stores.²⁰ In contrast, postoperative intravenous iron alone preserved iron stores during recovery from anemia,^{21,22} whereas postoperative iron plus EPO also resulted in increased reticulocyte counts during the first 2 postoperative weeks.²¹ In addition, the increase in Hb level from postoperative day 4 (nadir) to postoperative day 30 was 1 g/dL higher in patients who received intravenous iron supplements compared to those who received placebo.²¹

More recently, Karkouti et al²³ conducted a double-blind, placebo-controlled randomized study in patients undergoing cardiac (42%) or orthopedic surgery to determine if early recovery from severe postoperative anemia is accelerated by

Table 1 Effects of Perioperative Administration of Erythropoietin and Iron on Transfusion Requirements in Patients Undergoing Elective Cardiac Surgery

Study	+ EPO		Placebo		Iron (type, dose, days)	EPO† (IU/kg, route)
	n	% Transfused	n	% Transfused		
Kyo (1992) ⁸	40	50	16	75*	IV, 80–120 mg/wk, 4 wk	500–1,500, IV
Sowade (1997) ⁹	36	11	36	53*	Oral, 300 mg/d, 14 d	2,500, IV
D'Ambra (1997) ¹⁰	60	28	52	48	Oral, 975 mg/d, >8 d	1,200, SC
D'Ambra (1997) ¹⁰	59	32	52	48	Oral, 975 mg/d, >8 d	2,400, SC
Shimpo (1997) ¹¹	11 ^a	9	16 ^b	31	^a IV, NS, 4 d	600, IV
Shimpo (1997) ¹¹	21 ^a	0	16 ^b	31*	^b Oral, NS, 28 d	1,200, IV

Abbreviations: EPO, erythropoietin; IV, intravenous; NS, not stated; SC, subcutaneous.

*Reduction in both percentage of transfused patients and number of transfused units.

†EPO: total dose of recombinant human erythropoietin.

^aPatients receiving IV iron; ^bpatients receiving oral iron.

Table 2 Effects of Preoperative Autologous Blood Donation, With or Without Erythropoietin, on Transfusion Requirements in Patients Undergoing Elective Cardiac Surgery

Study	Control		PABD + rHuEPO		Iron (route)	EPO† (IU/kg, route)
	n	% Transfused (allogeneic)	n	% Transfused (allogeneic)		
Kiyama (1999) ¹²	16	100	16	25*	Oral ± IV	1,500, SC
Sonzogni (2001) ¹³	39	61	39	8*	Oral	1,000, SC + IV
Study	PABD		PABD + EPO		Iron (route)	EPO† (IU/kg, route)
	n	% Transfused (allogeneic)	n	% Transfused (allogeneic)		
Watanabe (1992) ¹⁴	14	29	12	0*	IV	1,400, IV
Watanabe (1992) ¹⁴	14	29	14	0*	Oral	1,200, SC
Kyo (1992) ⁸	5	40	62	21*	IV	600–1,900, IV
Schmoeckel (1993) ¹⁵	6	17	37	19	Oral	800–6,400, IV
Kulier (1993) ¹⁶	12	67	12	8*	Oral	1,600, SC
Hayashi (1994) ¹⁷	28	36	58	10*	Oral	600–1,200, SC
Walpoth (1996) ¹⁸	10	20	21	19	Oral	600–1,200, SC
Kobayashi (2001) ¹⁹	11	27	16	12	Oral	600, SC

Abbreviations: EPO, erythropoietin; IV, intravenous; PABD, preoperative autologous blood donation; SC, subcutaneous.

*Reduction in both percentage of transfused patients and number of transfused units.

†EPO: total dose of recombinant human erythropoietin.

intravenous iron therapy alone (n = 11) or in combination with EPO (n = 10), compared to oral iron (n = 10). They concluded that treatment with intravenous iron alone or in combination with EPO does not appear to accelerate early recovery from postoperative anemia, although reticulocyte counts and ferritin levels at postoperative day 7 were higher in the combination group and there was a trend towards lower transfusion requirements and better Hb recovery at postoperative day 42. However, the authors admitted several weaknesses in their study and did not exclude the possibility that higher doses or different timing of postoperative intravenous iron and EPO may be effective in accelerating correction of postoperative anemia.

Conclusions

In patients presenting for elective cardiac surgery, there is a high prevalence of anemia, which is linked to increase postoperative morbidity and mortality. Hence, preoperative anemia needs to be identified and evaluated early enough to implement the appropriate treatment.

Intravenous iron therapy, with or without EPO, may play an important role in the correction of perioperative anemia, as well as in facilitating PABD, thus reducing the risk of patient exposure to allogeneic blood transfusions.

Postoperative anemia is even more frequent than preoperative anemia, and systemic inflammation is probably the factor which impairs the effectiveness of oral iron therapy. Parenteral iron may act by treating decreased iron availability, thus increasing the action of both endogenous and exogenous erythropoietin. Although results are controversial, a faster reversion of anemia following intravenous iron injection might improve the quality of postoperative recovery.

As a short-term therapy, iron sucrose does not put the

patient at risk for long-term iatrogenic effects. However, large and well-conducted randomized controlled trials are needed to define more cost-effective intravenous iron and EPO regimens.

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