



Intravenous Iron in Colorectal Cancer Surgery

Manuel Muñoz,^a Arturo Campos,^b and José Antonio García-Erce^c

Patients requiring elective colorectal cancer surgery have a high prevalence of anemia and iron deficiency. Intravenous iron therapy, with or without recombinant erythropoietin (EPO), may play an important role in the correction of perioperative anemia and facilitate preoperative autologous donation, thus reducing the risk of patient exposure to allogeneic red blood cell (RBC) transfusion and improving patient outcomes. In addition, the use of intravenous iron allows for a significant reduction in EPO dose requirements. However, large and well-conducted randomized controlled trials are needed to define more cost-effective intravenous iron and EPO regimens. *Semin Hematol* 43(suppl 6):S36-S38 © 2006 Elsevier Inc. All rights reserved.

Anemia is one of the main signs of colorectal cancer. The incidence of anemia in these patients may vary from 25% to 70%, depending on the hemoglobin (Hb) cut-off, and is related to patient's age, tumor site and size, and Dukes stage.¹⁻³ However, more than half of these patients present with iron deficiency, with or without anemia, due to chronic blood loss, which in turn is related to tumor site and size.¹⁻³ Thus, anemia of chronic disease plus iron deficiency is a common finding in colorectal cancer.

On the other hand, it is well established that preoperative anemia is associated with increased requirements for allogeneic red blood cell (RBC) transfusion, which has been controversially linked to increased postoperative infection, recurrence rates, and mortality in patients with colorectal cancer, even after the introduction of universal leukoreduction.^{4,5} Longer hospital stays and higher health care costs have also been linked to allogeneic RBC transfusion.⁶ Thus, attempts have been made to reduce the use of transfusion in colorectal cancer patients using perioperative iron therapy with or without erythropoietin (EPO) administration and with or without preoperative autologous blood donation (PABD).

Perioperative Treatment With Iron and Erythropoietin

Okuyama et al⁷ studied 116 anemic patients (Hb \leq 10 g/dL) who underwent colorectal cancer surgery: 32 who received

oral iron supplementation (200 mg/d) for at least 2 weeks before surgery, and 84 who did not. Patients receiving iron had a significantly higher Hb level immediately before surgery and received fewer intraoperative RBC transfusions (9.4% v 27.4%; $P < .05$). In another study,⁸ 43 colorectal cancer patients received preoperative treatment with oral iron if they had a Hb greater than 14 g/dL and iron deficiency; iron sucrose (200 mg/wk) if Hb was 10 to 14 g/dL; or iron sucrose (200 mg twice per week) if Hb was less than 10 g/dL, during 2 to 3 weeks. Seventeen of these patients also received postoperative iron sucrose (200 mg on days 0, 2, and 4) in addition to the preoperative treatment. A retrospective series of patients not receiving iron was used as a control group ($n = 66$). Despite a lower baseline Hb (12.3 v 11.5 g/dL; $P < .05$), iron therapy reduced the transfusion index (4.0 v 1.3 units per patient; $P < .05$) and the percentage of patients who received preoperative transfusions (33% v 9%; $P < .05$), but not the percentage of patients administered perioperative transfusions (48% v 35%; $P = .161$). However, the treatment was ineffective in patients with a high transfusion index (>5 units per patient).⁸

Most probably, the effectiveness of perioperative iron treatment could be enhanced by concomitant EPO administration. Thus, in patients with moderate anemia (Hb >8.5 g/dL and ≤ 13 g/dL) scheduled for colorectal cancer surgery, perioperative treatment with EPO reduced the risk of exposure to allogeneic transfusion (100/263, 38% v 97/207, 47%) (relative risk [RR], 0.81; 95% confidence interval [CI], 0.61 to 1.00; $P = .054$), although there was great variability in total EPO dose and iron supplementation, as well as in outcomes (Table 1). Thus, EPO plus oral iron resulted in either no effect⁹ or a reduction in the number of transfused units only.^{10,11} In contrast, the administration of EPO plus intravenous iron resulted in a reduction of both the percentage of transfused patients and the number of transfused units.^{12,13}

^aGIEMSA, School of Medicine, University of Málaga, Málaga, Spain.

^bDepartment of Hematology, University Hospital "Virgen de la Victoria," Málaga, Spain.

^cDepartment of Hematology, University Hospital "Miguel Servet," Zaragoza, Spain.

Address correspondence to Manuel Muñoz, MD, PhD, GIEMSA, Facultad de Medicina, Universidad de Málaga, Campus de Teatinos, s/n, 29071 Málaga, Spain. E-mail: mmunoz@uma.es

Table 1 Effects of Perioperative Administration of Erythropoietin and Iron on Transfusion Requirements in Patients Undergoing Elective Colorectal Cancer Resection

Study	+ EPO		Placebo		Iron (type, dose, days)	EPO† (IU/kg, route)
	n	% Transfused	n	% Transfused		
Braga (1997) ¹²	10	10	10	50*	IV, 125 mg/d, 4 d	500, SC
Kettelhack (1998) ¹⁰	48	33	54	28	Oral, NS, 5–10 d pre IV, 40 mg, 1 d post	3,000–4,500, SC
Qvist (1999) ¹¹	38	34	43	54†	Oral, 200 mg/d, 4 d	1,350, SC
Kosmadakis (2003) ¹³	31	29	32	59*	IV, 100 mg/d, 14 d	4,200, SC
Christodoulakis (2005) ⁹	69	49	68	52	Oral, 200 mg/d, 10 d	1,800, SC
Christodoulakis (2005) ⁹	67	40	68	52†	Oral, 200 mg/d, 10 d	3,600, SC

Abbreviations: EPO, erythropoietin; IV, intravenous; SC, subcutaneous.

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

†Reduction in the number of transfused units only.

‡EPO: total dose of recombinant human erythropoietin.

Additionally, the use of intravenous iron allowed for a significant reduction in the total dose of EPO (Table 1). Similar results were reported by two small trials in 30 patients undergoing surgery for gastric cancer.^{14,15}

Preoperative Autologous Blood Donation

PABD is considered as one of the most safe and effective alternatives to allogeneic RBC transfusion in patients scheduled for surgical tumor resection. The results of four randomized controlled trials involving 1,067 patients undergoing colorectal cancer surgery showed that PABD significantly reduces allogeneic RBC transfusion requirements (RR, 0.44; 95% CI, 0.38 to 0.53; $P < .001$) (Table 2).^{16–19} However, the presence of anemia in many of these patients precludes their inclusion in a PABD program. Since perioperative treatment with EPO significantly increases Hb levels preoperatively, a combination of EPO and PABD seems a reasonable approach to reducing transfusion exposure in these patients. In fact, the result of two small trials (76 patients) showed a lower allogeneic transfusion rate in patients treated with PABD and EPO, compared to those treated with PABD alone (RR, 0.34;

95% CI, 0.14 to 0.85; $P < .012$).^{20,21} Again, the use of intravenous iron, as compared with oral iron, resulted in a reduction in the total dose of EPO oral iron (600 IU/kg v 2,200 IU/kg) (Table 2).

Conclusions

Patients requiring elective colorectal cancer surgery have a high prevalence of anemia and iron deficiency, which increases with patient age and tumor size, site, and stage.

Intravenous iron therapy, with or without EPO, may play an important role in the correction of perioperative anemia and facilitate PABD, thus reducing the risk of patient exposure to allogeneic RBC transfusion and improving patient outcomes. In addition, the use of intravenous iron allows for a significant reduction in EPO dose requirements.

Intravenous iron sucrose may be safely used in cancer surgical patients. As a short-term therapy, it 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.

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

Study	PABD		Control		Iron (route)	EPO† (IU/kg, route)
	n	% Transfused	n	% Transfused		
Hoyneck van Papendrecht (1992) ¹⁶	150	23	160	61*	Oral	—
Heiss (1993) ¹⁷	58	35	63	60*	Oral	—
Busch (1993) ¹⁸	239	28	236	56*	Oral	—
Vignali (1995) ¹⁹	53	4	108	44*	IV	—

Study	PABD		PABD + EPO		Iron (route)	EPO† (IU/kg, route)
	n	% Transfused	n	% Transfused		
Braga (1995) ²⁰	11	36	11	0*	IV	600, SC
Rau (1998) ²¹	26	39	28	18*	Oral	2,200, 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.

References

1. Sadahiro S, Suzuki T, Tokunaga N, Mukai M, Tajima T, Makuuchi H, et al: Anemia in patients with colorectal cancer. *J Gastroenterol* 33:488-494, 1998
2. Beale AL, Penney MD, Allison MC: The prevalence of iron deficiency among patients presenting with colorectal cancer. *Colorectal Dis* 7:398-402, 2005
3. Prutki M, Poljak-Blazi M, Jakopovic M, Tomas D, Stipancic I, Zarkovic N: Altered iron metabolism, transferrin receptor 1 and ferritin in patients with colon cancer. *Cancer Lett* 238:188-196, 2006
4. Li F, Kishida T, Kobayashi M: Serum iron and ferritin levels in patients with colorectal cancer in relation to the size, site, and disease stage of cancer. *J Gastroenterol* 34:195-199, 1999
5. Jensen LS, Puho E, Pedersen L, Mortensen FV, Sorensen HT: Long-term survival after colorectal surgery associated with buffy-coat-poor and leucocyte-depleted blood transfusion: A follow-up study. *Lancet* 365:681-682, 2005
6. Vamvakas EC, Carven JH: Allogeneic blood transfusion, hospital charges, and length of hospitalization: A study of 487 consecutive patients undergoing colorectal cancer resection. *Arch Pathol Lab Med* 122:145-151, 1998
7. Okuyama M, Ikeda K, Shibata T, Tsukahara Y, Kitada M, Shimano T: Preoperative iron supplementation and intraoperative transfusion during colorectal cancer surgery. *Surg Today* 35:36-40, 2005
8. Campos A, Sevilla I, Baca JJ, Romero A, Ramírez G, Muñoz M: Perioperative iron therapy and transfusion requirements in patients undergoing surgery for colon cancer. Preliminary results. *Transfusion Alternatives Transfusion Med* 7:96, 2005 (suppl, abstr)
9. Christodoulakis M, Tsiftsis DD, Hellenic Surgical Oncology Perioperative EPO Study Group: Preoperative epoetin alfa in colorectal surgery: A randomized, controlled study. *Ann Surg Oncol* 12:718-725, 2005
10. Kettelhack C, Hones C, Messinger D, Schlag PM: Randomized multicentre trial of the influence of recombinant human erythropoietin on intraoperative and postoperative transfusion need in anaemic patients undergoing right hemicolectomy for carcinoma. *Br J Surg* 85:63-67, 1998
11. Qvist N, Boesby S, Wolff B, Hansen CP: Recombinant human erythropoietin and hemoglobin concentration at operation and during the postoperative period: Reduced need for blood transfusions in patients undergoing colorectal surgery—Prospective double-blind placebo-controlled study. *World J Surg* 23:30-35, 1999
12. Braga M, Gianotti L, Gentilini O, Vignali A, Di Carlo V: Erythropoietic response induced by recombinant human erythropoietin in anemic cancer patients candidate to major abdominal surgery. *Hepatogastroenterology* 44:685-690, 1997
13. Kosmadakis N, Messaris E, Maris A, Katsaragakis S, Leandros E, Konstadoulakis MM, et al: Perioperative erythropoietin administration in patients with gastrointestinal tract cancer: prospective randomized double-blind study. *Ann Surg* 237:417-421, 2003
14. Tsuji Y, Kambayashi J, Shiba E, Sakon M, Kawasaki T, Mori T: Effect of recombinant human erythropoietin on anaemia after gastrectomy: A pilot study. *Eur J Surg* 161:29-33, 1995
15. Heiss MM, Tarabichi A, Delanoff C, Allgayer H, Jauch KW, Hernandez-Richter T, et al: Perisurgical erythropoietin application in anemic patients with colorectal cancer: A double-blind randomized study. *Surgery* 119:523-527, 1996
16. Hoynck van Papendrecht MA, Hop W, Langenhorst BL, Kothe FC, Marquet RL, Jeekel J: Feasibility of a predeposit autologous blood donation program in colorectal cancer patients: Results from a randomized clinical study. *Vox Sang* 62:102-107, 1992
17. Heiss MM, Mempel W, Jauch KW, Delanoff C, Mayer G, Mempel M, et al: Beneficial effect of autologous blood transfusion on infectious complications after colorectal cancer surgery. *Lancet* 342:1328-1333, 1993
18. Busch OR, Hop WC, Hoynck van Papendrecht MA, Marquet RL, Jeekel J: Blood transfusions and prognosis in colorectal cancer. *N Engl J Med* 328:1372-1376, 1993
19. Vignali A, Braga M, Dionigi P, Radaelli G, Gentilini O, Bellini A, et al: Impact of a programme of autologous blood donation on the incidence of infection in patients with colorectal cancer. *Eur J Surg* 161:487-492, 1995
20. Braga M, Gianotti L, Vignali A, Gentilini O, Servida P, Bordignon C, et al: Evaluation of recombinant human erythropoietin to facilitate autologous blood donation before surgery in anaemic patients with cancer of the gastrointestinal tract. *Br J Surg* 82:1637-1640, 1995
21. Rau B, Schlag PM, Willeke F, Herfarth C, Stephan P, Franke W: Increased autologous blood donation in rectal cancer by recombinant human erythropoietin (rhEPO). *Eur J Cancer* 34:992-998, 1998