Open Access

Optimal Iron Replacement for Colorectal Cancer-Induced Anaemia

Roderick J. Alexander*, Alison Alexander, Sue Surgenor, Elizabeth J. Williams and Guy F. Nash

Poole General Hospital, Longfleet Rd, Poole, Dorset BH15 2JB, UK

Abstract: *Introduction*: Iron deficiency anaemia (IDA) is commonly a result of colorectal cancer. Higher preoperative haemoglobin (Hb) is associated with an improved post-operative survival. The endpoint of normalising patients Hb is to reduce the need for perioperative blood transfusion which has oncological, safety and economic benefits.

Methods: This study aims to compare the overall effect and cost between oral iron and two forms of parenteral iron, in raising the Hb of 53 consecutive colorectal cancer patients with IDA. The pre- and post-treatment Hb were measuring over time for oral and two formulations of parenteral iron (CosmoFer® and Venofer®), as were the need for supplemental pre-operative blood transfusions. The Total Hb rise and Hb rise/day were calculated as was the overall cost (including blood transfusions) in each of the three iron supplementation groups.

Results: Both total Hb rise and Hb rise/day were significantly higher in the Venofer® (p=0.048, p=0.002) and CosmoFer® groups (p=0.034 & p=0.001) over oral iron. The oral iron group required significantly more blood than the Venofer® (p=0.04) and CosmoFer® groups (p=0.01). Although there was a trend for oral iron to cost more than parenteral, this did not reach significance.

Conclusions: This study suggests that the end point of transfusion reduction is possible by the increased Hb rise rate of Venofer® or CosmoFer®. In addition, parenteral iron supplementation is no more costly than the traditional oral route, taking into account blood transfusion requirement.

Keywords: Iron deficiency anaemia, parenteral iron, colorectal cancer.

INTRODUCTION

Iron deficiency anaemia (IDA) can be defined as a haemoglobin (Hb) of <110g/l in males, and <100g/l in females with microcytosis (Mean Cell Volume (MCV) <78fl and or ferritin <12ng/ml)[1]. Studies report up to 6.3% of all patients with IDA have colorectal cancer[2], and 60% of patients with colorectal cancer have IDA [3]. This figure rises to around 80% of patients with right sided colon cancer having IDA

Generally speaking, IDA is detrimental to colorectal cancer patients, in that a low Hb is linked with higher rates of peri-operative infections and an increased mortality in surgical patients [4]. The transfusion of blood in surgical patients can also be detrimental. Peri-operative blood transfusions are associated with an increased post-operative mortality [5], increased infective complication rate [6] and an increased risk of cancer recurrence; thought to be due to angiogenic stimulation [7] or an immunosuppressive effects of transfused packed red cells [8,9] There is also a financial cost to a blood transfusion with one unit of packed red cells costing £140 at our institution.

The Aim of this study is to compare the effect of oral iron and two forms of parenteral iron in raising the Hb and MCV of consecutive colorectal cancer patients with iron-deficiency anemia, and their respective effect on blood transfusion requirement.

We will also compare the overall costs of the three forms of iron supplementation, taking into account the need for blood transfusion.

METHODS

Out of 238 patients reviewed in our IDA clinic between September 2006 and April 2009, data was prospectively collected on 53 consecutive patients found to have colorectal cancer with IDA. They were initially treated pre-operatively with one of the following: Oral iron (Ferrous Sulphate 200mg twice daily), intravenous iron sucrose – 100mg 3 times per week for a maximum of 12 cycles (Venofer® Syner-Med Ltd, UK) or intravenous iron dextran as a once-only dose averaging 1100mg with a maximum of 20mg/kg. (CosmoFer® Vitaline Pharmaceuticals Ltd, UK.) The patients were not randomised into treatment groups in this study and were given the iron supplement available, depending on their diagnosis date and also pharmacy supply.

Each patients' pre- and post-iron treatment Hb's & MCV's were measured over time for the oral iron and the two forms of intravenous iron supplementation. The total Hb (g/l) and MCV (fl) rise over the course of treatment, the Hb rise per day (g/l/d) and the MCV rise per day (fl/d) were calculated and statistically analysed on an intention-to-treat basis, with two-tailed T-Tests.

The requirement for pre-operative transfusion was also noted and the overall cost (including blood transfusions) in each of the iron supplement groups, calculated. Data was again analysed with two-tailed T-Tests.

*Address correspondence to this author at the Poole General Hospital, Longfleet Rd, Poole, Dorset BH15 2JB, UK; Tel: +447776 256696; Fax: +441202 442615; E-mail: rodalexander@doctors.org.uk

1876-8202/10 2010 Bentham Open

Both blood transfusions and intravenous iron therapy require patients to be admitted to hospital for a short time. Thus, we have included the time spent in the Medical Investigation Unit (MIU) for those patients receiving infusions at a locally calculated rate of £43.80/hr in our cost analysis. Again, two-tailed T-Tests were used.

RESULTS

Out of the 53 patients included in this study, 23 received oral iron, 11 received Venofer® and 19 received CosmoFer®. Each group has comparable demographics with respect to mean age, sex distribution, cancer stage and site (Table **1**).

The majority of patients in this study had advanced cancers: 96% of all patients had T3/T4 lesions, with 59% having nodal disease and 19% having metastases (Table **1**). 74% of patients in this study had a right-sided colonic cancer (Table **1**).

The total Hb rise over the course of treatment was significantly more with Venofer® and CosmoFer®, compared with oral iron (p=0.048, p=0.034). (Fig. **1**). There was no significant difference in total Hb rise between Venofer® and Cosmofer® (p=0.82). There were no significant differences between the iron supplements with regard total MCV rise.

The Hb rise per day (taking in account treatment course length – Table **2**) was significantly more with Venofer® and CosmoFer®, compared with oral iron (p=0.002, p=0.001). (Fig. **2**). There was no difference in the Hb rise per day between Venofer® and CosmoFer® (p=0.16). Only CosmoFer® gave a significantly improved MCV rise/day over oral iron (Fig. **1**), and was significantly more than Venofer® (p=0.04).

A clear difference is observed in the mean treatment course length; oral iron – 52 days, Venofer® – 4.5days, CosmoFer® – 1day (Table **2**). Although Venofer® and CosmoFer® cost significantly more than oral iron, the oral iron group required significantly more blood than the Venofer® (p=0.04) or CosmoFer® groups (p=0.01) (Table **2** & Fig. **3**).

Although there was a trend for oral iron to cost more than either form of intravenous iron taking into account blood transfusion requirement; the difference in cost was not significant (Table **2** & Fig. **3**). There was also no significant difference in overall cost between the three treatment groups with the time needed in MIU added on (Table **2** & Fig. **3**).

DISCUSSION

Blood is certainly fast becoming our most precious resource, and especially so in surgery. Colorectal cancer patients in addition to many other solid tumors have long been reported to have reduced survival following blood transfusion. Chronic bleeding from the gastrointestinal tract results in iron deficiency, which ideally would be reversed by

Table 1. Group Demographics

	Oral Iron	Venofer	CosmoFer	Total	%
Number	23	11	19	**53**	
Mean Age-Yrs(range)	72 (33-90)	70 (51-80)	73 (54-88)		
Sex M:F	M=9 F=14	M=4, F=7	M=8, F=11		
Cancer Stage:					
T2	2 (9%)	0 (0%)	0 (0%)	2	**4**
T3	11 (48%)	3 (27%)	6 (32%)	20	**38**
T4	10 (43%)	8 (72%)	13 (68%)	31	**58**
N1	10 (43%)	4 (36%)	6 (32%)	20	**38**
N2	4 (17%)	6 (55%)	1 (5%)	11	**21**
METS	4 (17%)	2 (18%)	4 (21%)	10	**19**
Cancer Site:					
Ceacum	7	3	2	12	**23**
Ascending	9	4	12	25	**47**
Hepatic Flexure	0	0	1	1	**2**
Transverse	1	0	0	1	**2**
Splenic Flexure	0	1	0	1	**2**
Descending	1	0	1	2	**4**
Sigmoid	4	3	2	9	**17**
Rectum	1	0	1	2	**4**

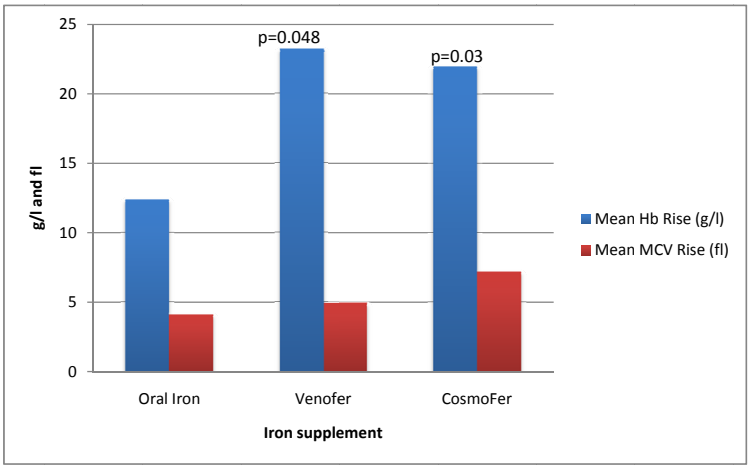

Fig. (1). Total Hb rise over the course of treatment with Venofer®, CosmoFer® and oral iron.

Table 2. Comparative Analysis of Iron Supplements

	Oral Iron	Venofer	CosmFer
Mean Course length (Days)	52	4.5	1
Mean total HB rise (g/l)	12.4	23.2	22
Mean total MCV rise (fL)	4.1	4.9	7.2
Mean Hb rise/day (g/l/d)	0.17	0.84	1.32
Mean MCV rise/day (fL/d)	0.05	0.18	0.42
Blood Transfusion Req.	44% (10/23)	9% (1/11)	11% (2/19)
Total No. Units	25	3	4
Mean Cost of Iron Supplement (£)	8.83	37.9	87.67
Mean cost (inc. Blood) (£)	162.01	76.01	117.08
Mean cost (inc. Blood & MIU) (£)	**257.22**	**295.01**	**345.31**

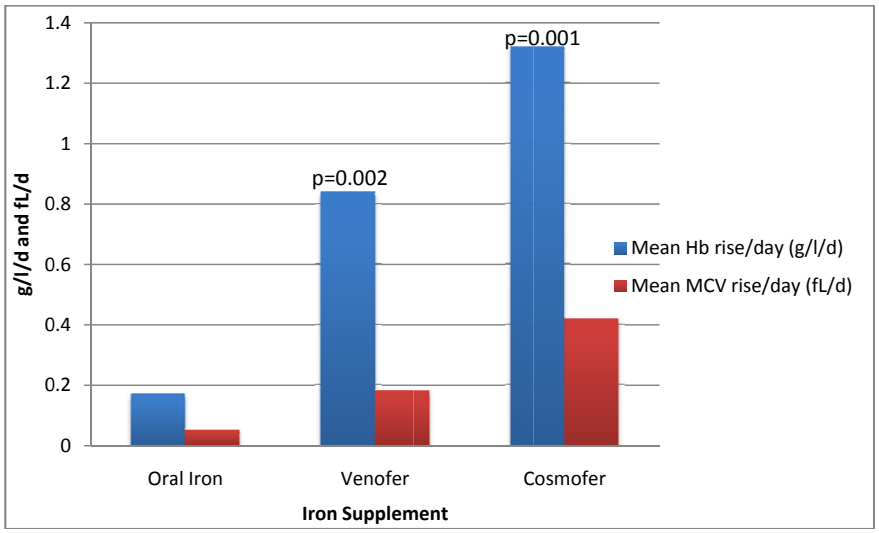

Fig. (2). Mean Hb and MCV rise /day with different iron supplements.

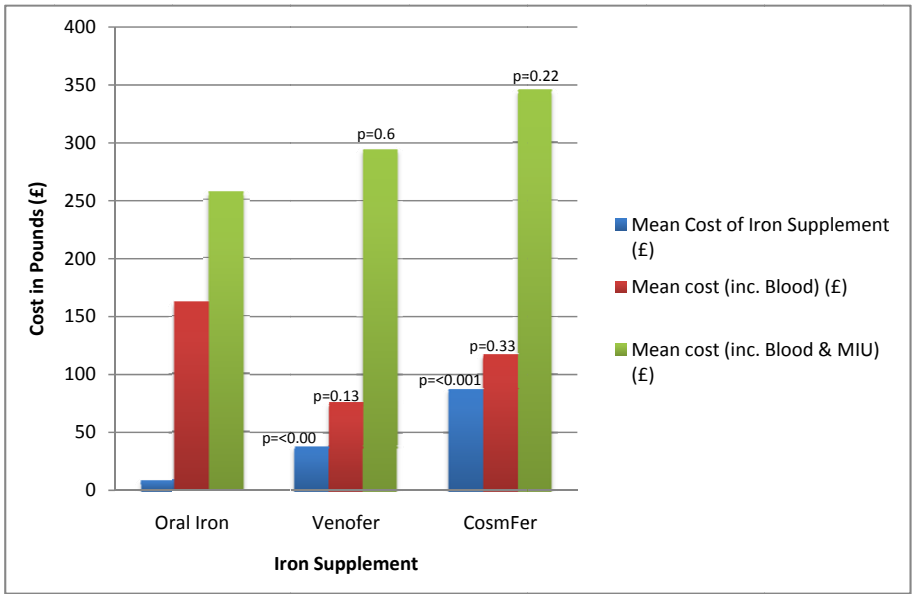

Fig. (3). Mean cost of iron supplements, including blood transfusion requirement and MIU day admission costs.

administration of iron rather than blood; as the risks of iron transfusion are dwarfed by the potential harm of receiving a blood transfusion.

Our study indicates that the end-point of pre-operative blood transfusion reduction in colorectal cancer patients is possible with the administration of pre-operative Venofer® or CosmoFer®, when compared with oral iron. Although the initial cost of both intravenous iron types are more than oral iron, this is balanced out by reduction in blood transfusion requirement in these groups resulting in no significant difference in cost overall.

There has been many studies indicating a benefit of intravenous iron in the treatment of anaemia associated with chronic kidney disease over oral iron [10-13]. Several observational studies indicate significant rises in Hb and reductions in transfusion requirement in pre-operative patients after administration of intravenous iron sucrose in patients undergoing arthroplasty [14,15] and hysterectomy [16]. A Spanish study including 84 patients reported a significant rise in haemoglobin of 1.6g/dl over 3-5 weeks pre-operatively in anaemic unselected surgical patients receiving intravenous iron sucrose [17].

In contrast, a recent randomised controlled trial comparing intravenous iron sucrose with placebo in the treatment of colorectal cancer-induced anaemia, reported no difference and no rise in pre-operative Hb and thus no benefit with iron sucrose in blood transfusion reduction [18]. In this study, 62 patients were randomised with 34 receiving 600mg of Venofer® in two divided doses of 300mg no less than 24hrs apart given a minimum of 15 days prior to surgery (average number of days or range was not stated in the article) [18]. Our dosing regimen for Venofer,® as recommended by the manufacturer, involves 100mg up to 3 times a week up to a maximum of 12 cycles. The average number of days from the first Venofer® administration to surgery in our study, was 27 days. These differences in methodology may account of the difference in results noted.

Little has been published using intravenous iron dextran in the treatment of pre-operative IDA. This may be due to early worries about high rates of anaphylaxis after administration [19]. Out of the 19 patients receiving CosmoFer® (Iron dexran) in our study, no one suffered an anaphylactic reaction.

In the perioperative period acute blood loss is possible and there are times that large tumors may bleed more than iron supplementation corrects the iron stores, in both of these examples blood transfusion is still perhaps inevitable.

As the majority of patients presenting with colorectal cancer are anaemic, it behoves the physician to be aware of the risks of blood and the potential alternatives including cosmoFer® and venofer®.

CONCLUSIONS

- Blood transfusion reduction in colorectal cancer-induced IDA is possible by the increased Hemoglobin rise-rate of Venofer® or CosmoFer® over oral iron supplementation.
- There is no increase in cost of parenteral over oral iron when taking into account blood transfusion requirement, in this cohort of patients.

Further studies on this topic may randomise between the three different iron supplementations used in our study with greater numbers of patients and possibly focus on cancer related outcomes of those patients who have avoided blood transfusion by prophylactically receiving iron.

REFERENCES

[1] National Referral Guidelines for Suspected Cancer. March 2000. Accessed Dec 5, 2009.www.dh.gov.uk/en/Publicationsandstatistics/Publications/PublicationsPolicyAndGuidance/DH_4008746

[2] Raje D, Mukhtar H, Oshowo A, Ingham Clark D. What proportion of patients referred to secondary care with iron deficiency anaemia have colon cancer? Dis Colon Rectum 2007; 50(8): 1211-4.

[3] Beale AL, Pennet MD, Allison MC. The prevalence of iron deficiency among patients presenting with colorectal cancer. Colorectal Dis 2005; 7(4): 398-402.

[4] Dunne JR, Malone D, Tracy JK, Gannon C, Napolitano LM. Perioperative anemia: an independent risk factor for infection, mortality, and resource utilization in surgery. J Surg Res 2002; 102(2): 237-44.

[5] Jagoditsch M, Pozgainer P, Klingler A, Tschmelitsch J. Impact of blood transfusions on recurrence and survival after rectal cancer surgery. Dis Colon Rectum 2006; 49(8): 1116-30.

[6] Houbiers JG, van de Velde CJ, van de Watering LM, *et al.* Transfusion of red cells is associated with increased incidence of bacterial infection after colorectal surgery: a prospective study. Transfusion 1997; 37: 126-134.

[7] Patel HB, Nasir FA, Nash GF, Scully MF, Kakkar AK. Enhanced angiogenesis following allogeneic blood transfusion. Clin Lab Haematol 2004; 26(2): 129-135(7).

[8] Amato A, Pescatori M. Perioperative blood transfusions for the recurrence of colorectal cancer. Cochrane Database Syst Rev 2006; 25(1): CD005033.

[9] Amato A, Pescatori M. Effect of perioperative blood transfusions on recurrence of colorectal cancer: meta-analysis stratified on risk factors. Dis Colon Rectum 1998; 41(5): 570-85.

[10] Charytoan, C, Qunibi W, Bailie GR, Venofer Clinical Studies Group. Comparison of intravenous iron sucrose to oral iron in the treatment of anemic patients with chronic kidney disease not on dialysis. Nephron Clin Pract 2005; 100(3): c55-62.

[11] Aggarwal HK, Nand N, Singh S, Singh M, *et al*. Comparison of oral versus intravenous iron therapy in predialysis patients of chronic renal failure receiving recombinant human erythropoietin. J Assoc Physicians India 2003; 51: 170-4.

[12] Agarwal R, Rizkala AR, Bastani B, *et al*. A randomised controlled trial of oral versus intravenous iron in chronic kidney disease. Am J Nephrol 2006; 26(5): 445-54.

[13] Charytan C, Qunibi W, Bailie GR. Comparison of intravenous iron sucrose to oral iron in the treatment of anemic patients with chronic kidney disease not on dialysis. Nephron Clin Pract 2005; 100(3): c55-62.

[14] Cuenca J, Garcia-Erce JA, Martinez F, Perez-Serrana L, Herrera A, Munoz M. Perioperative intravenous iron, with or without erythropoietin, plus restrictive transfusion protocol reduce the need for allogeneic blood after knee replacement surgery. Transfusion 2006; 46: 1112-9.

[15] Cuenca J, Garcia-Erce JA, Martinez AA, Solano VM, Molina J, Munoz M. Role of parenteral iron in the management of anaemia in the elderly patient undergoing displaced subcapital hip fracture repair: preliminary data. Arch Orthop Trauma Surg 2005; 125: 342-347.

[16] Diez-Lobo AI, Fisac-Martin MP, Bermejo-Aycar I, Munoz M. Preoperative intravenous iron administration corrects anemia and reduces transfusion requirement in women undergoing abdominal hysterectomy. Transfus Altern Med 2007; 9: 114-9.

[17] Muñoz M, García-Erce JA, Díez-Lobo AI, *et al*. Usefulness of the administration of intravenous iron sucrose for the correction of preoperative anemia in major surgery patients. Med Clin (Barc) 2009; 132(8): 303-6.

[18] Edwards TJ, Noble EJ, Durran A, Mellor N, Hosie KB. Randomised clinical trial of preoperative intravenous iron sucrose to reduce blood transfusion in anaemic patients after colorectal cancer surgery. Br J Surg 2009; 96: 1122-8.

[19] Van Wyck DB. Iron dextran in chronic renal failure. Semin Dialysis 1991; 4: 112-4.

Received: June 21, 2010 Revised: September 20, 2010 Accepted: September 28, 2010

© Alexander *et al.*; Licensee *Bentham Open.*

This is an open access article licensed under the terms of the Creative Commons Attribution Non-Commercial License (http://creativecommons.org/licenses/by-nc/3.0/) which permits unrestricted, non-commercial use, distribution and reproduction in any medium, provided the work is properly cited.