Original article

doi:10.1111/codi.12683

The feasibility and clinical efficacy of intravenous iron administration for preoperative anaemia in patients with colorectal cancer

B. D. Keeler*†[1], J. A. Simpson*†[1], S. Ng†, C. Tselepis‡, T. Iqbal§, M. J. Brookes‡¶ and A. G. Acheson*†

*Division of GI Surgery, University of Nottingham, Nottingham, UK, †Department of Colorectal Surgery, Nottingham University Hospitals NHS Trust, Nottingham, UK, ‡School of Cancer Sciences, University of Birmingham, Birmingham, UK, §Department of Gastroenterology, University Hospital Birmingham, Birmingham, UK and ¶Department of Gastroenterology, Royal Wolverhampton NHS Trust, Birmingham, UK

Received 27 February 2014; accepted 3 May 2014; Accepted Article online 10 June 2014

Abstract

Aim The study aimed to analyse the feasibility and efficacy of administration of a single intravenous iron infusion (IVI) in the preoperative optimization of colorectal cancer patients with anaemia.

Method Twenty patients were recruited at least 14 days before the planned date of surgery. A single 1000 mg dose of ferric carboxymaltose (Ferinject®) was administered as an outpatient procedure. Blood samples were taken at recruitment prior to drug administration (REC), on the day of surgery prior to any intervention (DOS) and on the first postoperative day. Allogeneic red blood cell transfusions (ARBT) and outcomes were recorded from recruitment throughout the study period.

Results There was a significant median rise in haemoglobin levels (Hb) from REC to DOS of 1.8 g/dl [interquartile range (IQR) 0.75–2.45, $P < 0.001$] for the entire cohort. Two patients received ARBT preoperatively, and for those not transfused preoperatively ($n = 18$), this incremental Hb rise remained significant ($P < 0.001$, median 1.65 g/dl, IQR 0.5–2.3). Of these patients, those who responded to IVI had higher erythropoietin (EPO) levels at recruitment ($P < 0.01$) and lower recruitment Hb values, transferrin-saturation (TSAT) and C-reactive protein (CRP) levels ($P < 0.05$). REC Hb ($R_s = -0.62$, $P < 0.01$), REC TSAT levels ($R_s = -0.67$, $P < 0.01$) and REC EPO ($R_s = 0.69$, $P < 0.01$) correlated with the magnitude of treatment change in Hb levels. Five patients received ARBT until the fourth postoperative day, which was significantly fewer than predicted ($P < 0.05$).

Conclusion IVI can be administered preoperatively in the outpatient clinic to colorectal cancer patients with anaemia, with associated reduction in ARBT use and increase in Hb levels.

Keywords Surgery, cancer, other

What does this paper add to the literature?
There are no published trials with clinical end-points reviewing the efficacy of preoperative intravenous iron (IVI) SOLELY in colorectal cancer patients with anaemia. Furthermore, there is debate about the efficacy of IVI in the preoperative optimization of these patients. This study aims to provide more evidence for this form of management.

Introduction

Anaemia is found in approximately 40% of patients diagnosed with colorectal cancer (CRC) [1]. It is associated with adverse postoperative outcome [2,3] and increased utilization of allogeneic red blood cell transfusion (ARBT) [4]. Furthermore, the perioperative use of ARBT in CRC surgery has also been associated with deleterious effects on the short- and long-term outcome [5].

The relationship between preoperative anaemia and adverse outcome has generated interest in the use of preoperative iron supplementation. Although preoperative intravenous iron (IVI) has been demonstrated to

Correspondence to: B. D. Keeler, Division of GI Surgery, University of Nottingham and Nottingham University Hospitals NHS Trust, Queen's Medical Centre, Nottingham NG7 2UH, UK.
E-mail: barriekeeler@doctors.org.uk

[1]The authors wish it to be known that, in their opinion, the first two authors should be regarded as joint first authors.

increase haemoglobin (Hb) levels in patients undergoing orthopaedic surgery [6], a clear role for iron supplementation has not been established in colorectal cancer patients with anaemia. Clinical trials have indicated oral iron to be effective at raising Hb levels preoperatively [7] and in reducing the preoperative fall in Hb levels between diagnosis and surgery [8] while reducing perioperative blood transfusion [7,8]. Despite a presumed superiority, IVI has been demonstrated to be ineffective in both these end-points in randomized trials [9].

This disparity may be in part due to hepcidin, a hormone that has been identified as a key regulator of iron handling, which reduces enteric iron absorption and systemic iron mobilization [10]. The hormone is of particular relevance in this context as CRC tumours are thought to induce the production of hepcidin [11] and serum hepcidin levels are proportional to CRC stage [12]. Drug development has resulted in IVI preparations that lend themselves to use in the colorectal surgical pathway. Test doses are no longer required, the incidence of anaphylaxis has been reduced and the drugs can be given in single, short infusions [13] which do not require prolonged monitoring.

This pilot study aimed to examine the feasibility of administration of a single 15-min IVI infusion given in an outpatient setting comparable to a preoperative assessment within the constraints of target operating waiting list times. Secondly, the study aimed to determine whether the infusion would result in a significant rise in the level of Hb and a decrease in ARBT. Furthermore, we aimed to identify potential predictors of response to therapy and hence propose methods for selecting candidates for treatment.

Method

Ethical approval was granted by Nottingham Research Ethics Committee (ref. no. 09/H0408/67) and the study was approved by the Medicines and Healthcare Products Regulatory Agency, UK (MHRA), ClinicalTrials.Gov reference NCT02057471.

Patient population

Anaemia was defined according the WHO definition (< 12 g/dl for women, < 13 g/dl for men) [14]. Twenty adult patients were identified and recruited from local CRC multidisciplinary meetings with histologically confirmed colonic or rectal adenocarcinoma with surgery planned as the primary treatment and who were also anaemic on a recent blood test. Patients were excluded if they had any contraindication to IVI therapy, as were patients given a date for surgery < 14 days after treatment would start. It was felt that a treatment effect may not be seen below this treatment period and could not be justified ethically. Patients with previous or current haematological disease and those unable to provide informed consent were also excluded. Written consent was obtained prior to any study intervention.

Intervention

Enrolled patients attended the hospital for one outpatient visit where initial blood tests were performed and IVI administered. If patients were taking oral iron supplements at recruitment, this was discontinued and the general practitioner informed. The IVI preparation, 1000 mg ferric carboxymaltose (Ferinject®, Vifor Pharma, Glattbrugg, Switzerland.) diluted in 250 ml of 0.9% normal saline was infused over 15 min under the supervision of a clinician, with a single blood pressure measurement taken before infusion to exclude preexisting hypotension. No other monitoring was performed, and a test dose was not required.

Blood collection

Blood was collected at recruitment (REC) prior to the iron infusion, on the day of surgery prior to any intervention (DOS) and on the first postoperative day (D1). Haematological testing of the blood was performed including full blood count for Hb and estimation of mean cell volume (MCV). Biochemical analysis measured serum ferritin, transferrin saturation (TSAT), C-reactive protein (CRP) and erythropoietin (EPO) levels. These tests were performed in the local NHS Trust laboratory, with the exception of EPO which was tested in line with local policy by transfer to NHS biochemistry laboratories in Dundee, UK.

Blood samples for hepcidin assay were centrifuged 1 h after collection and the serum stored at −80°C until the end of the study, whereafter the samples were analysed by mass spectrometry at the University of Birmingham, UK using the surface-enhanced laser desorption/ionization time-of-flight mass spectrometry method previously described [15].

Additional recording

Patient demographics, operative details, pathological staging of the tumour, blood transfusions up to discharge, complications and length of hospital stay were recorded, as was the cumulative iron deficit (CID). This is an estimation of the dose of iron required to treat iron-deficiency anaemia calculated using the Ganzoni equation (Fig. 1).

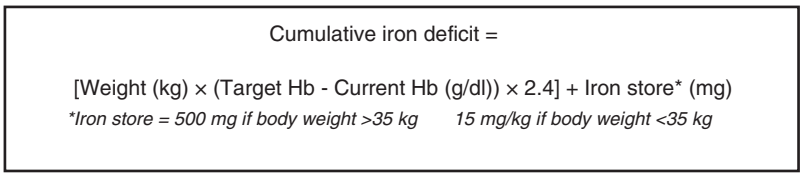

Figure 1 The Ganzoni equation for calculation of cumulative iron deficit (CID) (Hb, haemoglobin).

Patients were also assigned a transfusion 'trigger' point in line with local transfusion guidelines which are based upon the current UK Blood Transfusion and Tissue Transplantation Guidelines on the appropriate use of blood [16]. This decision was based upon patients' associated comorbidity, and resulted in two transfusion trigger groups: the first 'stringent' group (Group A) with a target of maintaining Hb above 7 g/dl, and the second group (Group B) for patients with associated cardiac or respiratory disease, with a target of 9 g/dl. The ultimate decision to administer blood transfusion remained at the discretion of the clinical team.

Using these transfusion points, a prediction model was employed to identify whether subjects would have received ARBT had IVI not been administered. The model was based on the assumption that the postoperative decrease in Hb between surgery and D1 was a constant nadir for each patient. Consequently, by subtracting the increase in Hb evident following IVI treatment from the acquired Hb levels after recruitment, it was possible to interpolate the Hb values of study subjects to D1 had IVI not been administered, and hence whether assigned transfusion thresholds would have been met without the IVI. These calculations are summarized in Fig. 2.

Statistical analysis

Response to treatment was defined as a 1.5 g/dL rise in Hb from recruitment to the day of surgery. This was selected on the basis of epidemiological studies which have indicated that over 80% of patients with anaemia diagnosed with CRC have a Hb level between 10 and 11.9 g/dl [1], hence correction of Hb by 1.5 g/dl would restore normal values in the majority of patients. The statistical level of significance for all tests was taken as $P = 0.05$. Nonparametric data were otherwise compared with the Wilcoxon signed rank test. Fisher's exact test was used to assess differences between predicted and actual ARBT administration. Correlations between variables and change in Hb with IVI treatment were estimated using Spearman's rank test and Pearson's product–moment method for nonparametric and parametric data, respectively. Statistical analysis was performed using SPSS® version 21 (SPSS, Chicago, Illinois, USA).

Results

Twenty patients (14 men) were recruited with a median age of 77 years [interquartile range (IQR) 73.5–79.8]. All received 1000 mg of ferric carboxymaltose, and there were no immediate adverse events associated with drug administration. Patient demographics, tumour details and operative data are illustrated in Table 1. The median duration of IVI treatment was 27.5 (IQR 16–43) days. Five patients had documented postoperative complications, including two respiratory infections, one anastomotic leakage, one port site hernia and a prolonged postoperative ileus. The median postoperative hospital stay was 7 (IQR 4.3–12) days.

Six patients received ARBT from recruitment until postoperative discharge, a total of 24 units transfused. Two were transfused preoperatively (5 units total), three were transfused on the day of surgery (7 units total) and three received ARBT postoperatively; all of those on or after postoperative Day 4 were associated with complications due to the operation (12 units). The details of all ARBT administered are available in Appendix S1 in Supporting Information. There was no association between transfusion rates and mode of operative access ($P = 0.303$).

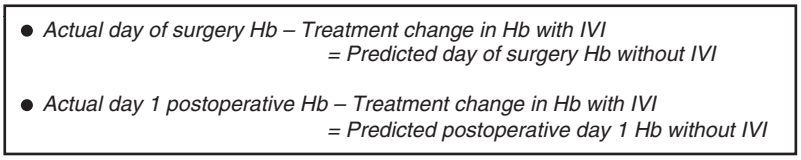

Figure 2 Calculation of predicted haemoglobin (Hb) levels (in g/dl) without intravenous iron (IVI) treatment.

Table 1 Patient demographics and operative details.

Gender	14 male (70)	6 female (30)
Age (years)	77 (36–85)	
Height (m)	1.7 (1.52–1.88)	
Weight (kg)	75 (56.2–105)	
Body mass index (kg/m^2)	25.9 (20.6–38.6)	
Recruitment Hb (g/dl)	9.25 (6.7–11.9) (male)	10.2 (4.6–11.7) (female)
Recruitment MCV (fl)	79.5 (67–94) (male)	85.5 (68–97) (female)
Recruitment CID (mg)	1583.7 (1043–1934) (male)	1399.4 (1194–1740) (female)
Patients taking oral Fe at recruitment	11 (55)	
Operation	Right hemicolectomy	11 (55)
	Anterior resection	6 (30)
	Extended right hemicolectomy	1 (5)
	Right hemicolectomy and sigmoid	1 (5)
	Colectomy Panproctocolectomy	1 (5)
Access	Laparoscopic	10 (50)
	Open	10 (50)
Tumour stage	T4	2 (10)
	T3	12 (60)
	T2	5 (25)
	T1	1 (5)
Nodal status	N2	1 (5)
	N1	3 (15)
	N0	16 (80)
Total length of stay (days)	7 (2–112)	

Patient details expressed as median and (range), with categorical operative details expressed as frequency and (percentage).

Eight patients were assigned to 'stringent' transfusion (Group A) and 12 to 'liberal' (Group B). The rationale for assignment to these groups is available in Appendix S2. In Group A, one patient received ARBT from recruitment up to the fourth postoperative day, with two predicted to require ARBT. Four patients within Group B were transfused over this period, while 11 patients were predicted to have required ARBT. The number of patients ($n = 5$) who received ARBT compared with those predicted to require ARBT without IVI ($n = 13$) was significantly different ($P < 0.05$).

In the entire cohort the median rise in Hb was 1.8 (IQR 0.75–2.45) g/dl. In patients not transfused preoperatively ($n = 18$), this increase was 1.65 g/dl and remained statistically significant (IQR 0.5–2.3 g/dl, $P < 0.001$). There were associated increases in Hb ($P < 0.001$) and TSAT ($P < 0.001$) and a reciprocal fall in EPO ($P < 0.001$) between recruitment and the day of surgery for those not transfused preoperatively. The changes in Hb are illustrated in Fig. 3 for those patients who were not transfused over the period illustrated.

For those patients not given ARBT preoperatively, 11 responded to IVI treatment and the responders had significantly higher EPO levels at recruitment ($P < 0.01$). Lower levels of CRP at recruitment ($P < 0.05$), TSAT values ($P < 0.05$) and Hb values ($P < 0.05$) were also evident in the responder group. There was no difference between the hepcidin levels of those who responded to treatment and those who didn't.

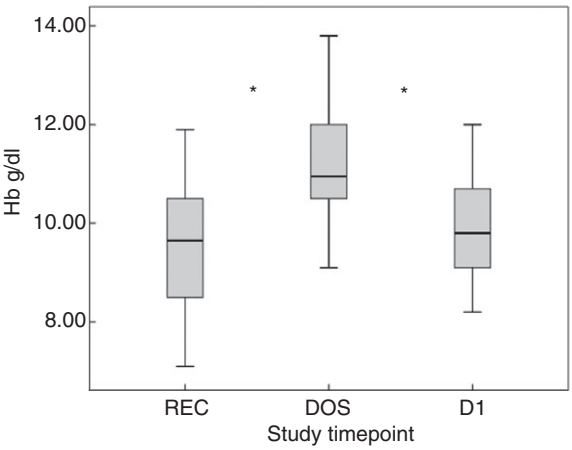

Figure 3 Haemoglobin (Hb) levels throughout the study. REC is the point of recruitment (prior to treatment), DOS is the day of surgery and D1 is the first postoperative day. *$P < 0.001$.

On further review of patients who were not transfused preoperatively, there was a positive correlation

between change in Hb with calculated CID ($R_s = 0.61$, $P < 0.01$) and also with EPO at recruitment ($R_s = 0.69$, $P < 0.01$). Conversely, an inverse relationship was seen between change in Hb and Hb at recruitment ($R_s = -0.62$, $P < 0.01$) and TSAT at recruitment ($R_s = -0.67$, $P < 0.01$) as illustrated in Fig. 4. Levels of CRP, hepcidin and ferritin at recruitment were not correlated with a change in Hb.

Discussion

The results from this study indicate that IVI therapy is a useful treatment in the preoperative optimization of CRC patients with anaemia. The drug was safely administered in the outpatient preadmission clinic without any associated adverse events, whilst conforming to patient treatment pathways and target waits. IVI therapy successfully raised Hb in patients with a median rise which would be expected to normalize the Hb of the majority of CRC patients with anaemia and was comparable to results from previous studies [6]. Furthermore, it appears that the IVI may have reduced the need for perioperative ARBT.

The authors recognize the limitations of the transfusion prediction model employed. The model assumes that without treatment the DOS Hb would at best equal the REC Hb. This potentially overestimates the actual DOS Hb as, without treatment, Hb levels would actually be expected to fall until the point of surgery. Furthermore, this assumption does not take into account the impact of oral iron supplementation which 55% of the patients were taking at the point of recruitment, and which may have been efficacious had it been continued [7].

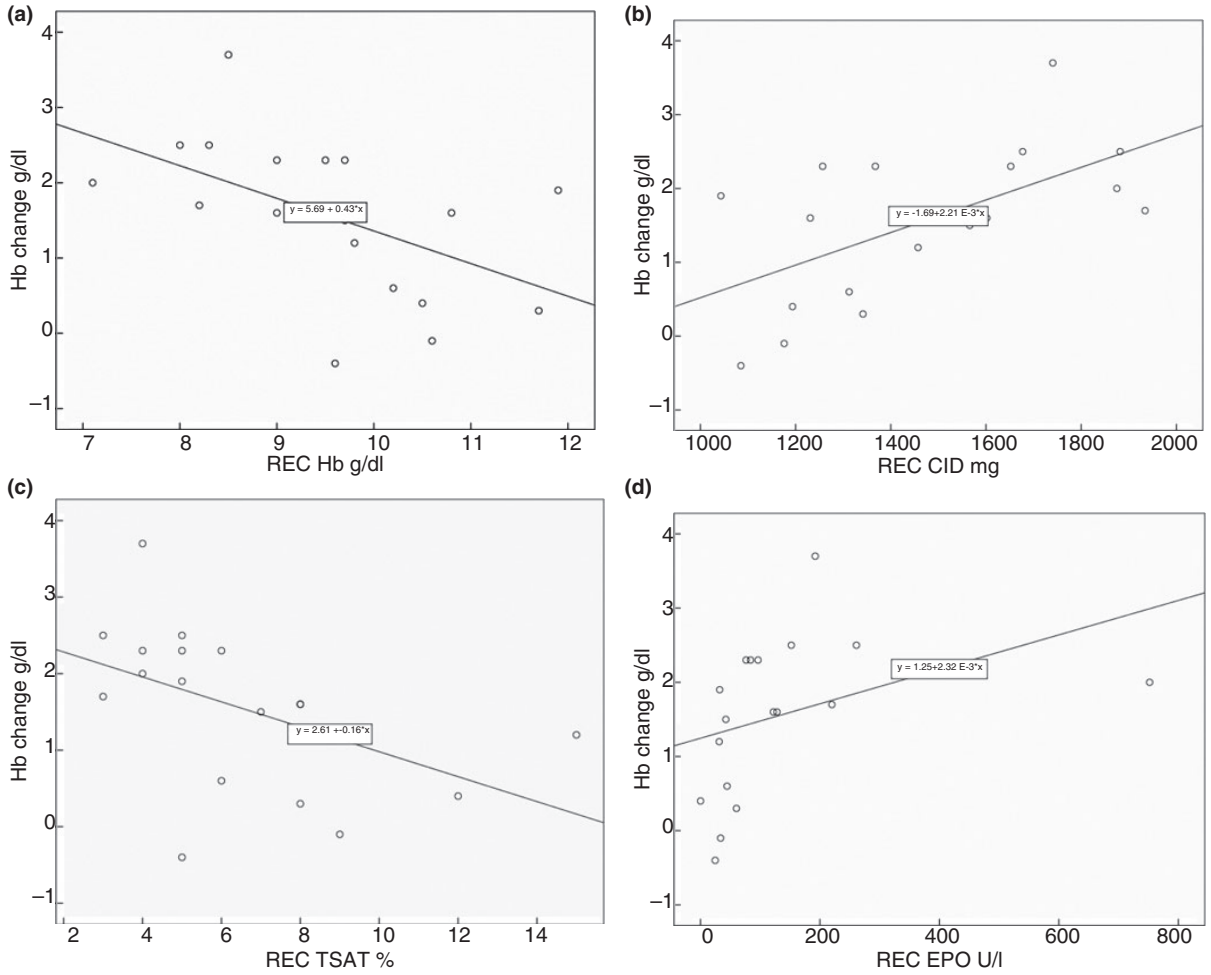

Figure 4 Scatterplot graphs to illustrate the change in haemoglobin (Hb) levels following therapy according to predictive parameters: (a) haemoglobin (REC Hb) at recruitment, (b) cumulative iron deficit (REC CID), (c) transferrin saturation at recruitment (REC TSAT), (d) erythropoietin at recruitment (REC EPO). All $P < 0.01$.

All patients in this study could have received a further dose of IVI based on the Ganzoni equation and the manufacturer's guidance, hence a larger response could potentially have been achieved. Despite this dose reduction, it appears that IVI increased Hb within the time frame of this study. The authors acknowledge that the median duration of treatment may be longer than feasible in other centres. From other large studies of IVI used to treat anaemia, it appears that the maximal Hb response is seen after 4–6 weeks [17]. Similarly, data suggest that patients with iron-deficiency anaemia will have used 91–99% of the iron from Ferinject® after 24 days [18], which needs to be factored in when optimizing the duration of treatment.

Furthermore, a maximum dose of 1 g of Ferinject® can be given per week and it appears that most patients will require more than one dose to achieve maximal effect. The importance of dose may be illustrated by the greater response to IVI seen in the present study than similar trials which used a smaller 600 mg dose of iron sucrose [9]. Consequently, an optimal treatment period is required in clinical practice, which will allow an adequate dose and a significant clinical response to justify the possible risks of IVI while not delaying surgery. Given the factors and logistical issues discussed, this interval is unlikely to be < the 2 weeks employed in this study but it does warrant further investigation.

This study also reviewed potential predictive biomarkers which may predict the magnitude of response to IVI in raising Hb levels before surgery. It is interesting to note that the Hb level at recruitment predicted the subsequent response to IVI, given historical data which have demonstrated similar findings with oral iron [19]. As CID is calculated from this value, the correlation between CID and change in Hb is also a logical association, as is the inverse relationship evident with TSAT.

In the present study hepcidin failed to identify responders to treatment in contrast to the findings of similar studies using oral iron [20]. This may either reflect the smaller numbers of patients involved in the study or it may be a consequence of multifactorial influences on hepcidin levels which include inflammation and cancer [11,12]. As hepcidin influences enteric iron absorption and mobilization of iron from the reticuloendothelial system, it is possible that hepcidin levels are more relevant in predicting the absorption and subsequent response to oral iron rather than systemic mobilization of IVI, or that levels are more reflective of tumour biology and stage than iron status. The predictive role of hepcidin still needs further study.

Endogenous EPO levels at recruitment were also significantly higher in patients who respond to IVI and also correlated with the Hb response to IVI. Co-administration of exogenous EPO with IVI has been proposed in other preoperative settings [21] but is not clearly advocated for malignancy, partly owing to data which suggest that administration of EPO stimulates tumour recurrence [22]. In conclusion IVI can be administered effectively before CRC surgery and appears to increase Hb levels significantly and reduce the requirement for ARBT. The increase in Hb levels appears to have been greater than increments seen in similar studies using oral iron in this context.

Conflict of interest

A.A.'s research department has received grant support from Syner-Med, UK, Vifor Pharma, Switzerland, and Pharmacosmos A/S, Denmark. He has received honoraria or travel support for consulting or lecturing from the following companies: Ethicon Endosurgery, Johnson and Johnson Ltd, UK; Olympus, Essex, UK; and Vifor Pharma Ltd, Glattbrugg, Switzerland. He is an advisory board member for Pharmacosmos A/S, Denmark.

M.B.'s research department has received grant support from Syner-Med, UK, and Vifor Pharma, Switzerland. He has received honoraria or travel support for consulting or lecturing from the following companies: Vifor Pharma Ltd, Glattbrugg, Switzerland; Merck Sharp & Dohme Limited, UK. M.B. is also an advisory board member to Vifor International and to Sanofi UK.

Author contributions

Study conception and design: AA, MB, AS, CT, TI. Acquisition of data: SN, AS, CT, BK. Analysis and interpretation of data: BK, AS. Writing manuscript: BK, AS, CT, TI, MB, AA

References

1 Ludwig H, Van Belle S, Barrett-Lee P *et al.* The European Cancer Anaemia Survey (ECAS): a large, multinational, prospective survey defining the prevalence, incidence, and treatment of anaemia in cancer patients. *Eur J Cancer* 2004; **40:** 2293–306.

2 Leichtle SW, Mouawad NJ, Lampman R, Singal B, Cleary RK. Does preoperative anemia adversely affect colon and rectal surgery outcomes? *J Am Coll Surg* 2011; **212:** 187–94.

3 Carson JL, Duff A, Poses RM *et al.* Effect of anaemia and cardiovascular disease on surgical mortality and morbidity. *Lancet* 1996; **348:** 1055–60.

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:** 237–44.
5 Acheson AG, Brookes MJ, Spahn DR. Effects of allogeneic red blood cell transfusions on clinical outcomes in patients undergoing colorectal cancer surgery: a systematic review and meta-analysis. *Ann Surg* 2012; **256:** 235–44.
6 Khalafallah AA, Abdul MA, Chan J *et al.* A prospective randomized controlled trial to assess the effect of intravenous versus oral iron therapy in the treatment of orthopaedic preoperative anaemia. *J Blood Disord Transfus* 2012; **3:** 127–33.
7 Quinn M, Drummond RJ, Ross F, Murray J, Murphy J, Macdonald A. Short course pre-operative ferrous sulphate supplementation is it worthwhile in patients with colorectal cancer? *Ann R Coll Surg Engl* 2010; **92:** 569–72.
8 Lidder PG, Sanders G, Whitehead E *et al.* Pre-operative oral iron supplementation reduces blood transfusion in colorectal surgery - a prospective, randomised, controlled trial. *Ann R Coll Surg Engl* 2007; **89:** 418–21.
9 Edwards TJ, Noble EJ, Durran A, Mellor N, Hosie KB. Randomized 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.
10 Zhang X, Rovin BH. Beyond anemia: hepcidin, monocytes and inflammation. *Biol Chem* 2013; **394:** 231–8.
11 Ward DG, Roberts K, Brookes MJ *et al.* Increased hepcidin expression in colorectal carcinogenesis. *World J Gastroenterol* 2008; **14:** 1339–45.
12 Roberts K, Ward DG, Brookes MJ *et al.* Hepcidin expression relates to colorectal tumour stage. *Gastroenterology* 2008; **134:** 447.
13 Auerbach M, Ballard H. Clinical use of intravenous iron: administration, efficacy, and safety. *Hematology Am Soc Hematol Educ Program* 2010; **2010:** 338–47.
14 WHO. *Haemoglobin concentrations for the diagnosis of anaemia and assessment of severity.* Geneva, Switzerland: World Health Organistaion, 2011.
15 Ward DG, Roberts K, Stonelake P *et al.* SELDI-TOF-MS determination of hepcidin in clinical samples using stable isotope labelled hepcidin as an internal standard. *Proteome Sci* 2008; **6:** doi: 10.1186/1477-5956-6-28.
16 UKBT. United Kingdom Blood Transfusion and Tissue Transplantation Guidelines. http://www.transfusionguidelines.org.uk/index.aspx 2012 [cited 2014 February].
17 Evstatiev R, Marteau P, Iqbal T *et al.* FERGIcor, a randomized controlled trial on ferric carboxymaltose for iron deficiency anemia in inflammatory bowel disease. *Gastroenterology* 2011; **141:** 846–53 e2
18 Beshara S, Sorensen J, Lubberink M *et al.* Pharmacokinetics and red cell utilization of 52Fe/59Fe-labelled iron polymaltose in anaemic patients using positron emission tomography. *Br J Haematol* 2003; **120:** 853–9.
19 Freire WB. Hemoglobin as a predictor of response to iron therapy and its use in screening and prevalence estimates. *Am J Clin Nutr* 1989; **50:** 1442–9.
20 Bregman DB, Morris D, Koch TA, He A, Goodnough LT. Hepcidin levels predict nonresponsiveness to oral iron therapy in patients with iron deficiency anemia. *Am J Hematol* 2013; **88:** 97–101.
21 Cladellas M, Farre N, Comin-Colet J *et al.* Effects of Preoperative Intravenous Erythropoietin Plus Iron on Outcome in Anemic Patients After Cardiac Valve Replacement. *Am J Cardiol* 2012; **110:** 1021–6.
22 Pascual M, Bohle B, Alonso S *et al.* Preoperative administration of erythropoietin stimulates tumor recurrence after surgical excision of colon cancer in mice by a vascular endothelial growth factor-independent mechanism. *J Surg Res* 2013; **183:** 270–7.

Supporting Information

Additional Supporting Information may be found in the online version of this article:

Appendix S1. Details of patients who received ARBT during the admission for surgery.

Appendix S2. The comorbidity rationale for assignment of each patient to transfusion trigger groups.