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Pre-operative oral iron supplementation reduces blood transfusion in colorectal surgery – a prospective, randomised, controlled trial

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ABSTRACT

INTRODUCTION Allogeneic blood transfusion confers a risk to the recipient. Recent trials in colorectal surgery have shown that the most significant factors predicting blood transfusion are pre-operative haemoglobin, operative blood loss and presence of a transfusion protocol. We report a randomised, controlled trial of oral ferrous sulphate 200 mg TDS for 2 weeks' pre-operatively versus no iron therapy.

PATIENTS AND METHODS Patients diagnosed with colorectal cancer were recruited from out-patient clinic and haematological parameters assessed. Randomisation was co-ordinated via a telephone randomisation centre.

RESULTS Of the 49 patients recruited, 45 underwent colorectal resection. There were no differences between those patients not receiving iron (n = 23) and the iron-supplemented group (n = 22) for haemoglobin at recruitment, operative blood loss, operation duration or length of hospital stay. At admission to hospital, the iron-supplemented group had a higher haemoglobin than the non-iron treated group (mean haemoglobin concentration 13.1 g/dl [range, 9.6–17 g/dl] versus 11.8 g/dl [range, 7.8–14.7 g/dl]; P = 0.040; 95% CI 0.26–0.97) and were less likely to require operative blood transfusion (mean 0 U [range, 0–4 U] versus 2 U [range, 0–11 U] transfused; P = 0.031; 95% CI 0.13–2.59). This represented a cost reduction of 66% (47 U of blood = £4700 versus oral $FeSO_4$ at £30 + 15 U blood at £1500). At admission, ferritin in the iron-treated group had risen significantly from 40 µg/l (range, 15–222 µg/l) to 73 µg/l (range, 27–386 µg/l; P = 0.0036; 95% CI 46.53–10.57).

CONCLUSIONS Oral ferrous sulphate given pre-operatively in patients undergoing colorectal surgery offers a simple, inexpensive method of reducing blood transfusions.

KEYWORDS

Ferrous sulphate – Colorectal – Surgery – Anaemia – Transfusion

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Colorectal cancer is the third most common cancer in the UK.[1] Rates of peri-operative transfusion ranging from 20–75% have been reported in patients undergoing colorectal resection.[2,3] Despite innovations in transfusion medicine, peri-operative transfusion of allogeneic blood components has inherent risks including immunomodulation, transmission of disease, allergic reaction, and allo-immunisation. More recently, the introduction of leukocyte-depleted blood has led to an increased cost pressure on health resources.

Studies have shown that predictors of increased peri-operative transfusion are proximal tumours, increasing tumour size, operative blood loss and pre-operative anaemia.[2,4,5] Pre-operative anaemia is a frequent finding in this group of surgical patients and accounts for a substantial number of blood transfusions. Defining anaemia as a haemoglobin of less than 13.5 g/dl in men and 11.5 g/dl in women, locally recorded data from the preceding years' 223 surgical colorectal cancer patients demonstrated that 51% of men and 25% of women were anaemic (38% combined) on admission. The overall transfusion rate in the men and women was 28% and 41%, respectively, whereas in the anaemic patients it was 39% and 68%, respectively.

The aim of this study was to assess whether pre-operative oral iron therapy would decrease pre-operative anaemia and, thereby, reduce the incidence of peri-operative transfusion.

Patients and Methods

The study received approval from the Plymouth Healthcare Trust Local Research Ethics Committee.

Patients diagnosed with colorectal cancer were identified in out-patient clinics. All patients fit for surgery were

Table 1 Local transfusion protocol

Haemoglobin	Action
> 10 g/dl	No transfusion
8–10 g/dl	Transfuse if:
	Abnormal ECG
	Ischaemic heart disease
	Obstructive lung disease
	Consultant's discretion
	Unable to absorb oral iron
< 8 g/dl	Transfuse to target 10 g/dl

eligible. Following written informed consent, patients were randomised (by telephone to a distant centre) to receive ferrous sulphate 200 mg TDS until surgery (group 1) or standard clinical management (group 2).

The clinical team (surgeons, nurses, anaesthetists) were blinded to treatment allocation. The collection of data was performed by a research fellow not involved in the direct care of the patient, and gathered from the clinical notes. It was not possible to use a placebo and blind the patient, as oral iron alters stool colour.

Postoperatively, patients underwent standard care including adherence to a transfusion protocol (Table 1). We did not feel protocol-driven intra-operative haematocrit alone would be an accurate indicator of need for transfusion; therefore, although transfusion usually followed protocol, this was at the anaesthetist's discretion.

Haemoglobin, ferritin, and reticulocyte count were assessed in clinic, on admission, on the first postoperative day and at discharge. Duration of surgery, type of surgery, tumour TNM stage, estimated blood loss, blood transfusion requirements and length of stay were recorded.

Statistical analysis

In order to detect a change in haemoglobin of 0.5 g/dl with a SD of 0.5 g/dl, power of 80% and two-tailed significance of 0.05, $n = 10$. In recruiting 20 anaemic patients, we anticipated seeing 52 (20x100/38) in total.

Data were analysed with SPSS v.11 and assessed for normality using Shapiro-Wilk test. Continuous data were analysed using the Student's *t*-test (paired and unpaired) or Mann-Whitney U and Wilcoxon signed ranks tests depending on the distribution of the data. Proportional data were analysed using the chi-squared or Fisher's exact test. All analysis was performed on an intention-to-treat basis with $P < 0.05$ taken as being significant. Data are expressed as either median (range) or mean (SD), depending on the distribution.

Table 2 Patient demographics

	Iron group ($n = 24$)	No-iron group ($n = 25$)
Age (years)	69 (47–89)	72 (57–80)
Sex	14M, 8F	14M, 9F
Anaemic patients	3M, 3F	8M, 6F
Operation duration (min)	139 (60–210)	133 (73–240)
Estimated blood loss (ml)	800 (188–6919)	600 (200–3500)
Duration iron treatment (days)	14 (12–56)	N/A
Dukes' staging		
A	1	3
B	8	7
C	13	11

Ranges given in parentheses.

No significant difference between groups except in proportion of

Results

In total, 49 patients with colorectal malignancies were recruited (iron, $n = 24$; no-iron $n = 25$). Two patients from each group were deemed unsuitable for resective surgery at admission, two underwent stent insertion and two were referred to the palliative care team.

There was no significant difference between the two groups in terms of age, sex, operative procedure, operative duration, estimated blood loss, or tumour stage (Tables 2 and 3).

Table 3 Type of operation by group

Operation	Iron group ($n = 23$)	No-iron group ($n = 22$)
Anterior resection	12	13
A-P resection	2	1
Left hemicolectomy	2	0
Right hemicolectomy	5	8
Subtotal colectomy	0	1
Hartmann's procedure	1	0

No significant differences.

Table 4 Haematological variables at recruitment and at admission

	Group	Recruitment	Admission	*P*-value [95% CI]
Haemoglobin (g/dl); mean (SD)				
	Iron group	13.4 (1.9)	13.1 (2.0)*	NS
	No-iron group	12.4 (2.1)	11.8 (2.0)*	0.002 [0.26–0.97]
Ferritin (mg/l); median (range)				
	Iron group	40 (15–222)	73 (27–386)	0.001 [10.57–46.53]
	No-iron group	43 (6–293)	43 (4–414)	NS
Reticulocyte count (x 10^9/l); median (range)	Iron group	36 (21–112)	41 (28–93)	NS
	No-iron group	50 (3–91)	49 (3–136)	NS

*Significant difference between groups in admission haemoglobin ($P = 0.04$).

At recruitment, there was no significant difference between the two groups in haemoglobin concentration, ferritin levels, and reticulocyte count (Table 4). Between recruitment and admission, the haemoglobin concentration fell in both groups, although this was only significant in the no-iron group (paired *t*-test, $P = 0.002$; 95% CI 0.26–0.97; Table 4).

Between recruitment and admission, the ferritin level in the iron treated group increased from 40 µg/l (range, 15–222 µg/l) to 73 µg/l (range, 27–386 µg/l; paired *t*-test, $P = 0.004$; 95% CI 46.53–10.57; Table 4). At admission, the iron-supplemented group had a significantly higher haemoglobin than the non-iron treated group, 13.1 g/dl (SD, 2.0 g/dl) and 11.8 g/dl (SD, 2.0 g/dl), respectively, (unpaired *t*-test, $P = 0.04$; 95% CI 2.51–0.06; Table 4).

Peri-operatively, a significant proportion of patients in the no-iron group (56%; $n = 13$) received allogeneic transfusions in comparison with the iron-supplemented group (27%; $n = 6$; $\chi^2 = 3.943$; $P = 0.0471$]. The iron-treated group collectively received 15 U, the no-iron group 47 U (median, 0 U; range, 0–4 units versus 2 U; range, 0–11 U, respectively; unpaired *t*-test, $P = 0.031$; 95% CI 0.13–2.59; Table 5).

Discussion

Colorectal patients constitute a major group of recipients of blood as they form a large section of the surgical population. After establishment of a transfusion protocol, there are three factors which determine transfusion levels: blood loss, starting haemoglobin level, and age.[2,5] Much interest has centred on methods of blood conservation, ranging from blood salvage recovery equipment to pre-operative donation. Unfortunately, recovery is not suitable in malignancy and autologous transfusion is often precluded by pre-existing anaemia secondary to the underlying colonic neoplasm. Affects of acute normovolaemic haemodilution have been

Table 5 Blood transfusion requirements

	Group	Number patients transfused (%)	Total units transfused	Median units transfused (range)	*P*-value [95% CI]
All patients					
	Iron group (23)	6 (26%)	15	0 (0–4)	0.031 [0.13–2.59]
	No-iron group (22)	13 (59%)	47	2 (0–11)	
Anaemic patients					
	Iron group (6)	3 (50%)	6	1 (0–2)	NS
	No-iron group (14)	10 (71.4%)	39	2.5 (0–11)	

investigated, but transfusion rates are not reduced in colorectal surgical patients.[2]

This randomised, controlled, pilot study of 45 patients indicates that pre-operative ferrous sulphate administration lessens the fall in haemoglobin experienced by patients awaiting surgery for colorectal cancer (Table 4). In a centre operating a transfusion protocol, iron-supplemented patients received less peri-operative allogeneic blood transfusions, despite greater intra-operative blood losses.

This study was designed to investigate the effects of oral iron treatment on patients undergoing elective colorectal resections. The proportion of anaemic patients matched predicted levels (44% versus 38%) and results show a benefit of oral iron treatment for all patients. The reasons for this are unclear but may be related to improved haemopoeisis. Another consideration is optimal duration of iron treatment. In this study, the median length of treatment was 14 days (range, 12–56 days) but studies are required to determine whether a longer treatment period would be more beneficial for patients.

Oral iron is a safe, simple and inexpensive intervention. Increasing concern over transmission of vCJD in blood products has driven recent blood donation legislation, further limiting potential blood donors. These measures will increase the financial and supply burden and impact heavily on the future management of all patients undergoing major elective surgery.

The financial implications of this intervention are appreciable. A fortnight's course of ferrous sulphate 200 mg TDS currently costs the National Health Service £1.30. A single, allogeneic unit of blood costs £100 excluding extraneous costs such as giving sets and nursing care. In this study population, 47 U were transfused in the non-iron supplemented patients amounting to a total cost of £4700. In comparison, the iron-supplemented patients cost £1530 ($FeSO_4$ at £30 + 15 U at £1500) representing a 66% cost reduction.

Previous research has suggested that the poorer outcome reported in association with transfusion is related to operative blood losses or factors causing the bleeding, which extend patient recovery time.[6–8] Patients given pre-operative oral iron supplements were discharged from hospital earlier than the non-intervention group (median length of stay 11.5 days [range, 6–35 days] in no-iron group, 10 days [range, 6–26 days] in the iron group; not significant). This may, in part, be secondary to the reduced level of transfusion.

Although this trial was externally randomised, the proportion of anaemic patients on recruitment into the trial was higher in the no-iron group, which we cannot explain. The difference in transfusion requirements for the two groups may, therefore, represent a type I statistical error. However, the objective assessment of a greater fall in haemoglobin in the no-iron group demonstrates the beneficial effect of oral iron.

Conclusions

If the conclusions of this pilot study are reproducible in a large, placebo-controlled, randomised trial, the impact on clinical management of anaemic surgical and oncological patients will be immense. Further research is now urgently required, not only to assess the impact of iron supplementation in reducing peri-operative transfusion, but its impact on other markers of favourable outcome such as length of stay, morbidity and mortality.

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