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Short course pre-operative ferrous sulphate supplementation – is it worthwhile in patients with colorectal cancer?

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ABSTRACT

INTRODUCTION Pre-operative anaemia is well recognised in patients presenting with colorectal cancer (CRC). While the benefits of long-term $FeSO_4$ supplementation on Fe deficiency anaemia are well established, it is not known if short-course supplementation (2–3 weeks) impacts significantly on pre-operative haemoglobin (Hb) levels. This study examines the impact of short-term, oral $FeSO_4$ supplementation on patients undergoing surgery for CRC.

PATIENTS AND METHODS All patients with CRC presenting to a single surgeon were included. At diagnosis, baseline Hb and blood film were checked on all patients who then received 200 mg tds of $FeSO_4$. Haemoglobin was rechecked pre-operatively and daily postoperatively. Patients requiring pre-operative blood transfusions were excluded from analysis.

RESULTS Between 1 January 2004 and 31 December 2006, 117 patients were identified, 14 of whom were excluded. Patients received a median of 39 days' treatment with $FeSO_4$. Fifty-eight (56.3%) patients were anaemic at presentation gaining a mean of 1.73 g/dl ($P < 0.001$) from short-course $FeSO_4$ supplementation. Right-sided tumours (lower mean Hb at presentation; $P = 0.008$) responded more to $FeSO_4$ when compared to left-sided tumours ($P < 0.017$). Increase in Hb was unrelated to pathological stage. The transfusion rate for all curative resections was 0.69 units/patient. For the historical cohort (patients undergoing curative resection between 1 January 2001 and 31 December 2003), the mean transfusion rate fell from 1.69 units/patient.

CONCLUSIONS Routine short-course supplementation with iron offers improved pre-operative Hb prior to surgery in CRC, especially in right-sided lesions and those with presenting anaemia.

KEYWORDS

Colorectal cancer – $FeSO_4$ supplementation – Anaemia – Haemoglobin

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Approximately 36,000 cases of colorectal cancer (CRC) are diagnosed per year in the UK.[1] It is the third most common form of cancer among both males and females, and the second most common cause of cancer mortality in the UK. Pre-operative anaemia is well recognised in patients presenting with colorectal cancer, with recent series suggesting a prevalence of iron deficiency in 60%[2] and an associated anaemia in up to 38%[3] of new presentations.

Pre-operative anaemia is recognised as a predictive factor for blood transfusion,[4,5] as well as a predictor of adverse outcomes in surgical patients. Carson *et al.*[6] demonstrated that overall mortality increases as the haemoglobin concentration decreases, with even mild anaemia conferring an increased death risk.

As well as becoming an increasingly scarce commodity, allogeneic blood transfusion confers potential risks to the recipient including immunomodulation, transfusion reaction and disease transmission. Peri-operative blood transfusion with allogeneic blood is also suggested to increase the risk of postoperative infectious complications.[7,8] A recent meta-analysis of 36 studies supports the evidence that peri-operative blood transfusion has a detrimental effect on the recurrence of curable colorectal cancers although a direct causal relationship cannot be proven.[9]

While the benefits of long-term ferrous sulphate supplementation on iron-deficiency anaemia are well established, it is not known if short-course supplementation (2–3 weeks) impacts significantly on pre-operative haemoglobin levels

and the resultant transfusion rate in all patients. We also questioned whether pre-operative administration of oral ferrous sulphate even in patients who were not anaemic would result in a reduction in the overall transfusion requirements. This cohort study was, therefore, designed to assess the impact of short-course $FeSO_4$ supplementation on the incidence of pre-operative anaemia and peri-operative transfusion in patients presenting with colorectal carcinoma.

Patients and Methods

Ethical committee approval was granted for a cohort study only. It was considered to be unethical to randomise anaemic patients to a group where they would not receive a therapy of proven benefit.

All elective patients presenting to a single surgeon with a diagnosis of colorectal cancer between 1 January 2004 and 31 December 2006 were included. Baseline full blood count (FBC), including haemoglobin level, was checked at the time of first presentation to the colorectal service. All patients were commenced on a standard dose of oral iron supplementation ($FeSO_4$ 200 mg three times daily; generic preparation) regardless of presenting haemoglobin levels. Haemoglobin levels were rechecked immediately prior to surgery and, on a daily basis, postoperatively. All surgical interventions were standard open procedures performed by the same surgeon with no change in practice throughout the study period or historical cohort. Diathermy dissection (Ethicon Bi-Polar) was employed throughout all procedures in the study and historical cohorts.

All allogeneic transfusions both intra-operatively and during the postoperative stay were identified both prospectively and confirmed retrospectively using both case-note review and the hospital blood bank transfusion database. Indication for postoperative transfusion remained standard for hospital protocol which remained unchanged throughout the study period and also historical controls. Haemoglobin < 8 g/dl was considered to be indication for transfusion. Blood transfusion at Hb levels greater than 8 g/dl may only be given in exceptional circumstances, such as symptomatic cardiac ischaemia.

Tumour site (right sided vs left sided and rectal) was recorded for each patient, as well as Dukes' stage.

Patients requiring pre-operative blood transfusion due to symptomatic anaemia were excluded from analyses as this would not adequately reflect the effect of ferrous sulphate administration. Patients undergoing surgery with palliative intent were also excluded from analyses.

For the purposes of analysis, patients were considered to be anaemic if their Hb level was below that of the hospital's sex-dependent reference ranges (male 13.5–18.0 g/dl, female 11.5–16.5 g/dl). Continuous data were analysed using Student's *t*-test and Mann–Whitney U-test, where appropriate. Proportional data were analysed using the chi-squared test or Fisher's exact test. All analyses were performed using SPSS v13.0 with $P < 0.05$ considered significant.

A historical cohort consisting of patients attending between 1 January 2001 and 31 December 2003 ($n = 167$), together with transfusion rates, was identified from a prospectively maintained database in order to assess the impact on our unit transfusion rate. The historical cohort underwent surgery by the same surgeon with no change in transfusion criteria or intra-operative technique between cohorts. As with the current study group, patients undergoing palliative resection or receiving pre-operative transfusions were excluded from this cohort. There was no significant difference in tumour location ($P = 0.68$), age at presentation ($P = 0.16$), or tumour stage ($P = 0.14$).

Results

During a 3-year period, 117 patients were identified for inclusion in the study cohort. Fourteen patients were excluded due to the requirement for pre-operative transfusion as a result of symptomatic anaemia. Of the remaining patients, 63.1% ($n = 65$) were male and 36.9% ($n = 38$) were female. Median age was 68 years (range, 44–88 years) in the male group and 62 years (range, 37–86 years) in the female group. Of the patients, 23.3% had a right-sided tumour, with 26.2% left-sided and 48.5% rectal.

Patients received a median of 39 days (IQR 7–63 days) treatment with $FeSO_4$ prior to surgery. Median time to surgery from date of diagnosis/presentation was also 39 days (IQR 7–63 days).

Fifty-eight (56.3%) patients were anaemic at the time of presentation (Table 1). The remaining patients had Hb levels within the hospital sex-dependent reference ranges. No patients were found to be polycythaemic. Those patients who were anaemic exhibited a greater benefited from short course $FeSO_4$ supplementation, gaining a mean of 1.73 g/dl when compared to the normochromic group (mean gain of 0.46 g/dl; $P < 0.001$, Mann–Whitney U-test).

Patients with right-sided tumours were more likely to be anaemic at presentation ($P = 0.036$, chi-squared test) and presented with a lower initial mean Hb (10.7 g/dl) when compared to left-sided and rectal tumours (12.4 g/dl; $P = 0.008$, Student's *t*-test; Table 2). Patients with right-sided tumours also had a greater response to $FeSO_4$ (mean increase of 1.61 g/dl) compared to the left-sided group (mean increase 0.93 g/dl; $P = 0.017$, Mann–Whitney U-test). We considered short-course treatment to be less than 14 days administration, with a mean increase of 0.9 g/dl in all patients treated for less than 2 weeks prior to surgery (Table 3). Longer course therapy was considered to be greater than 14 days administration.

There was no statistical difference in baseline Hb or increase when stratified by pathological stage.

Table 1 **Increase in haemoglobin (Hb) between presentation and surgery**

	All patients (n = 103)		Anaemic (n = 58)		Non-anaemic (n = 45)	
	Mean	IQR	Mean	IQR	Mean	IQR
Presentation Hb (g/dl)	12.0	10.0–13.9	10.2	9.0–12.0	14.0	13.3–14.8
Pre-operative Hb (g/dl)	13.1	11.6–14.6	11.9	10.9–13.4	14.5	13.6–15.5
Increase (g/dl)	1.1	$P < 0.001$	1.7	$P < 0.001$	0.5	$P < 0.001$

Table 2 **Right-sided versus left-sided tumours response to ferrous sulphate**

	Right-sided (n = 24)		Left-sided/rectal (n = 79)	
	Mean	IQR	Mean	IQR
Presentation Hb (g/dl)	10.7	7.7–12.9	12.4	10.8–14.2
Pre-operative Hb (g/dl)	12.4	11.1–13.5	13.3	12.1–14.8
Increase (g/dl)	1.7	$P < 0.001$	0.9	$P < 0.001$

Table 3 **Response to ferrous sulphate by duration of treatment**

	< 14 days (n = 30)		> 14 days (n = 73)	
	Mean	IQR	Mean	IQR
Presentation Hb (g/dl)	11.8	9.9–13.4	12.1	10.5–14.2
Pre-operative Hb (g/dl)	12.7	11.4–14.0	13.3	12.0–14.9
Increase (g/dl)	0.9	$P = 0.001$	1.2	$P < 0.001$

A total of 10 patients required intra-operative transfusion with a further 10 requiring postoperative transfusion. Two patients with a haemoglobin greater than 8.0 g/dl (8.1 g/dl and 10.7 g/dl, respectively) were transfused postoperatively due to symptomatic condition. A total of 71 units of blood (red cell concentrate) were used in our study cohort resulting in a mean transfusion rate for all curative resections of 0.69 units/patient. This compares with the historical cohort (curative resection between 1 January 2001 and 31 December 2003) of 1.69 units/patient. This represents a reduction in transfusion rate of 54% between the two cohorts.

Discussion

These results demonstrate that short-course ferrous sulphate supplementation is effective in raising the pre-operative haemoglobin level in patients presenting with colorectal cancer. This effect is particularly noticeable in those patients with anaemia at the time of presentation, and those with right-sided tumours. Despite a more significant increase in the anaemic subgroup, patients who were normochromic at presentation appeared to benefit also, with a mean Hb increase of 0.46 g/dl. The overall incidence of anaemia (56.3%) in our patient population appears to be higher than noted in the literature,[10] which may reflect our patient population. The proportions by tumour location are similar (right vs left vs rectal; 75% vs 56% vs 48%). Two similar studies have previously been conducted. Okuyama *et al.*[11] identified 116 anaemic patients from a cohort of 569, 32 of whom received iron supplementation and the remaining 84 did not. The iron group were less likely to require an intra-operative transfusion. Lidder *et al.*[12] randomised 45 patients to receive iron supplementation for 2 weeks prior to surgery. This reduced transfusion rate in the intervention group.

The transfusion rate (units/patient) between the two observed cohorts fell by greater than 50% during the study

period. Other than the introduction of short-course $FeSO_4$ supplementation at the time of diagnosis, no other significant changes in process, protocol or technique occurred during this time.

With the use of routine $FeSO_4$ supplementation, a total of 12 patients fell within the 'transfusion zone' postoperatively. Assuming all other factors including intra-operative blood loss remained constant and that patients' haemoglobin levels would not increase spontaneously between the times of diagnosis and surgery, we can predict that 31 patients would have fallen into this category had they not received supplementation.

No patients suffered adverse side-effects or reactions to $FeSO_4$ during the study period with no significant reports of change in bowel habit. No patients discontinued therapy due to side-effects following administration. We acknowledge that use of $FeSO_4$ may incur problems with adequate preparation for patients undergoing colonoscopy; however, this was not encountered within our cohort as patients were commenced on $FeSO_4$ following diagnosis.

Study limitations

We are limited by our study design to compare our treated cohort, with that of a historical control group. This was due to ethical concerns over withholding a proven treatment for anaemia by randomising anaemic patients into a group in which they purposefully be denied what is considered to be best practice. Additionally, as patients were treated on an out-patient basis, it was difficult to assess full compliance with supplementation by any means other than patient testimony, despite all patients confirming their continued administration of $FeSO_4$ as prescribed.

Conclusions

Despite the documented shortcomings, our study demonstrates that short-course supplementation with $FeSO_4$ in patients with colorectal cancer is a safe and economic method of increasing pre-operative haemoglobin level and may reduce the intra-/postoperative transfusion requirements.

Acknowledgement

Martha Quinn and Robert J Drummond contributed equally to this study.

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