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Ferric carboxymaltose infusion versus oral iron supplementation for preoperative iron deficiency anaemia in patients with colorectal cancer (FIT): a multicentre, open-label, randomised, controlled trial

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Summary

Background A third of patients with colorectal cancer who are eligible for surgery in high-income countries have concomitant anaemia associated with adverse outcomes. We aimed to compare the efficacy of preoperative intravenous and oral iron supplementation in patients with colorectal cancer and iron deficiency anaemia.

Methods In the FIT multicentre, open-label, randomised, controlled trial, adult patients (aged 18 years or older) with M0 stage colorectal cancer scheduled for elective curative resection and iron deficiency anaemia (defined as haemoglobin level of less than 7·5 mmol/L (12 g/dL) for women and less than 8 mmol/L (13 g/dL) for men, and a transferrin saturation of less than 20%) were randomly assigned to either 1–2 g of ferric carboxymaltose intravenously or three tablets of 200 mg of oral ferrous fumarate daily. The primary endpoint was the proportion of patients with normalised haemoglobin levels before surgery (≥12 g/dL for women and ≥13 g/dL for men). An intention-to-treat analysis was done for the primary analysis. Safety was analysed in all patients who received treatment. The trial was registered at ClincalTrials.gov, NCT02243735, and has completed recruitment.

Findings Between Oct 31, 2014, and Feb 23, 2021, 202 patients were included and assigned to intravenous (n=96) or oral (n=106) iron treatment. Treatment began a median of 14 days (IQR 11–22) before surgery for intravenous iron and 19 days (IQR 13–27) for oral iron. Normalisation of haemoglobin at day of admission was reached in 14 (17%) of 84 patients treated intravenously and 15 (16%) of 97 patients treated orally (relative risk [RR] 1·08 [95% CI 0·55–2·10]; p=0·83), but the proportion of patients with normalised haemoglobin significantly increased for the intravenous treatment group at later timepoints (49 [60%] of 82 *vs* 18 [21%] of 88 at 30 days; RR 2·92 [95% CI 1·87–4·58]; p<0·0001). The most prevalent treatment-related adverse event was discoloured faeces (grade 1) after oral iron treatment (14 [13%] of 105), and no treatment-related serious adverse events or deaths were observed in either group. No differences in other safety outcomes were seen, and the most common serious adverse events were anastomotic leakage (11 [5%] of 202), aspiration pneumonia (5 [2%] of 202), and intra-abdominal abscess (5 [2%] 202).

Interpretation Normalisation of haemoglobin before surgery was infrequent with both treatment regimens, but significantly improved at all other timepoints following intravenous iron treatment. Restoration of iron stores was feasible only with intravenous iron. In selected patients, surgery might be delayed to augment the effect of intravenous iron on haemoglobin normalisation.

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Introduction

Preoperative anaemia affects up to a third of patients undergoing resection for colorectal cancer.[1,2] Despite the increased risk of mortality, length of stay, and complications associated with preoperative anaemia, it is unclear if correction of anaemia produces a corresponding correction in the associated risk to patients in terms of perioperative morbidity.[3–6]

Cancer-related anaemia is a multifactorial problem caused by impaired iron absorption from the gut, impaired iron availability, blood loss, and deficiency of multiple nutrients.[7] Iron deficiency anaemia is the most common type of anaemia in patients with colorectal cancer.[8,9] Having sufficient iron stores is necessary for adequate erythropoiesis and is an essential component of many other metabolic enzymes involved in basic cellular processes and mitochondrial function.[10–12]

Preoperative iron deficiency anaemia can be treated with iron supplementation. Despite the association of anaemia with adverse outcomes of colorectal surgery,

Research in context

Evidence before this study

We searched PubMed using the terms ("intravenous iron" OR "oral iron") AND "anaemia" AND "surgery" with no language or date restrictions on June 1, 2022. Previous studies were mainly done in orthopaedic and cardiac surgeries and focused on reducing allogenic blood transfusion. This might not be a relevant outcome in colorectal surgery because the incidence of transfusion is low and is more likely to be associated with the complexity of the surgery rather than the preoperative haemoglobin level. Transfusion is also less suitable for patients with colorectal cancer because it is associated with cancer recurrence. A 2019 Cochrane review including six randomised controlled trials (RCTs) was difficult to interpret due to the large heterogeneity in iron regimens, the inclusion of patients with and without anaemia, and the use of thresholds for haemoglobin normalisation other than those recommended in WHO guidelines. An RCT from 2000 comparing intravenous iron and placebo for major abdominal surgery included a wide variety of indications, hampering extrapolation of the results to daily practice. The efficacy of intravenous versus oral iron in patients with colorectal cancer and with iron deficiency anaemia currently remains unknown.

Added value of this study

This study is the first RCT to provide data on the efficacy of intravenous and oral preoperative iron supplementation in patients with colorectal cancer to improve preoperative haemoglobin levels and iron stores, together with clinical outcome variables (eg, complications, reinterventions, and postoperative stay). The results show that both intravenous and oral iron do not normalise haemoglobin levels just before surgery, but intravenous iron increases haemoglobin levels significantly more effectively during follow-up. Only intravenous iron was shown to be able to reverse iron deficiency, and in patients with mild anaemia, the rate of postoperative reinterventions and admission to intensive care units were lower after intravenous iron compared with oral iron, indicating that sufficient iron stores might be more important than haemoglobin levels.

Implications of all the available evidence

In the FIT study, the increased haemoglobin levels, restored iron stores, and improved clinical outcomes observed postoperatively in a well defined group of patients with colorectal cancer after intravenous iron compared with oral iron suggest a potential benefit of intravenous iron preoperatively. Other available literature is indefinite due to heterogeneity in study design and outcomes. Restoration of iron stores is feasible with intravenous iron, justifying intravenous iron infusion as part of a prehabilitation programme for patients undergoing colorectal surgery to reduce postoperative negative sequelae. In selected patients, surgery might be delayed for 3 weeks to augment the effect of intravenous iron on haemoglobin normalisation.

there is relative undertreatment of preoperative iron deficiency anaemia.[3–6] A possible explanation for this undertreatment is that the need for acute perioperative blood transfusion is only around 4% in colorectal cancer surgery.[2] However, even a mild preoperative anaemia is associated with an increased risk of morbidity and 30-day mortality.[6,13] Iron deficiency can also occur in the presence of normal haemoglobin levels, causing fatigue and impaired physical and cognitive functioning.[11,12] Another explanation for the undertreatment of iron anaemia might be that the time until surgery is perceived to be insufficient for preoperative optimisation of haemoglobin levels. Intravenous iron increases haemoglobin levels faster than oral iron supplementation, but requires an infusion, sometimes necessitating an extra hospital visit. Studies in other surgical populations have shown that haemoglobin normalisation can be accomplished in a few weeks in patients scheduled for gynaecological surgery.[14]

A 2019 Cochrane review comparing different iron regimens found no clear advantage of any type of iron treatment, but the review was difficult to interpret due to heterogeneity in design of the included studies.[15] A 2020 randomised controlled trial (RCT) comparing intravenous iron and placebo for major abdominal surgery found no difference in postoperative blood transfusions.[16] One RCT comparing intravenous iron and usual care in patients undergoing major abdominal surgery found lower blood transfusion rates after intravenous iron.[17] Both studies included a wide variety of indications, which makes it difficult to extrapolate results to specific patient groups. Patients with colorectal cancer undergoing surgery are particularly at higher risk of having specific iron deficiency anaemia, especially right-sided tumours, and have additional issues with oral iron absorption. One RCT comparing oral and intravenous iron in patients with colorectal cancer and anaemia found no difference in blood transfusion rates, but did find that intravenous iron resulted in restored iron stores and correction of anaemia, but this study used different cutoffs for anaemia and included patients without iron deficiency.[18]

There is no strong evidence regarding the efficacy of iron supplementation in patients with colorectal cancer who have a narrow preoperative time period, and there is no consensus on the optimal treatment strategy in the preoperative setting. We therefore aimed to compare the efficacy of intravenous and oral iron supplementation for correction of anaemia in patients with iron deficiency anaemia before elective colorectal cancer surgery. We hypothesised that intravenous iron would lead to a higher percentage of patients with a normalised haemoglobin level (≥7·5 mmol/L [12 g/dL] for women and ≥8 mmol/L [13 g/dL] for men) at the day of surgery, compared with oral iron.

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Methods

Study design and participants

See Online for appendix

FIT was an international, multicentre, open-label, randomised, controlled superiority trial, done in 14 centres in the Netherlands and one centre in Italy (appendix p 18), investigating which type of iron administration is superior in the treatment of iron deficiency anaemia in patients with colorectal cancer undergoing surgery. Details on the protocol were published earlier.[19] Available literature at the time of conception of this study appeared to show a benefit of both oral and intravenous iron, and we considered it unethical to include a placebo group that would withhold optimal treatment from these patients. Ethical approval was gained before this trial from the medical ethical committee of Amsterdam UMC, location University of Amsterdam, and from all local ethical committees in participating centres. All patients provided written informed consent before trial participation.

For more on **Alea** see https://www.aleaclinical.eu/

Patients aged 18 years or older were eligible if planned for curative resection for M0 stage colorectal cancer and with a proven iron deficiency anaemia, without the need for immediate blood transfusion according to local protocol. Iron deficiency anaemia was defined as haemoglobin level of less than 7·5 mmol/L (12 g/dL) for women and less than 8 mmol/L (13 g/dL) for men,[20] and a transferrin saturation of less than 20%. Exclusion criteria were palliative surgery or metastasised disease; blood transfusion within 1 month before screening; serum ferritin more than 800 µg/L; pregnancy; contraindication to use ferric carboxymaltose or ferrous fumarate; American Society for Anesthesiology classification score of more than 3; the use of erythropoietin stimulating drugs within 3 months before screening; chronic kidney disease (glomerular filtration rate <30 mL/min per 1·73 m²); myelodysplastic syndrome; elevated liver enzymes (>3 times the normal value); hereditary hemochromatosis; thalassaemia; and haemolytic anaemia or chronic haemolysis. Detailed inclusion and exclusion criteria are shown in the appendix (p 2).

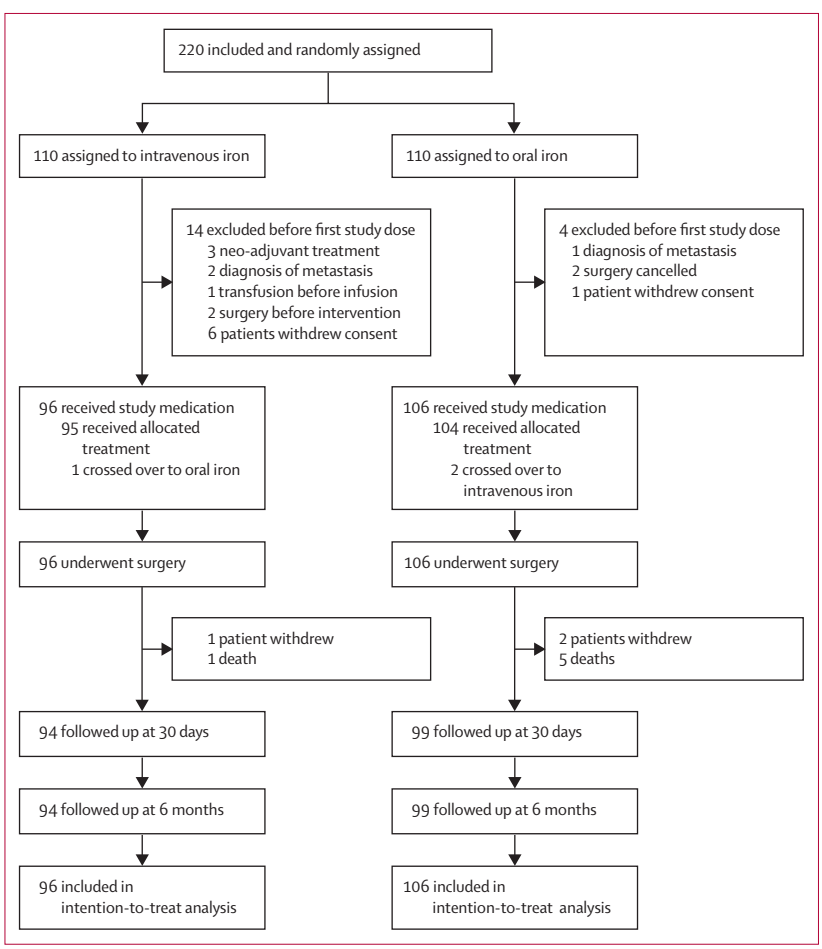


Figure 1: **Trial profile**

Randomisation

Patients were screened, informed, and asked to sign informed consent in the outpatient clinic of the participating centre by local study personnel. Patients were then computer randomised (1:1) in random block sizes of two or four for either intravenous or oral iron with an online web-based tool (Alea) by the study personnel at the initiating study site. Randomisation was stratified for age, colon or rectal carcinoma, open or laparoscopic operation, and baseline haemoglobin levels (5·0–6·2 mmol/L [8–10 g/dL] *vs* 6·3–8·0 mmol/L [10–13 g/dL]). Patients and treating physicians were not masked to the outcome of the randomisation, because it was not deemed feasible.

Procedures

Details of the study procedures are in the appendix (p 2). Iron treatment was initiated as soon as possible following randomisation. Patients who received ferric carboxymaltose were given doses according to the summary of product characteristics depending on body-weight and haemoglobin level. Patients with severe anaemia (haemoglobin ≤6·2 mmol/L [10 g/dL]) received a dose of 1500 mg if their weight was 35–70 kg and 2000 mg if it was more than 70 kg. Patients with mild anaemia (haemoglobin >6·2 mmol/L [10 g/dL]) received a dose of 1000 mg if their weight was 35–70 kg and 1500 mg if it was more than 70 kg. A maximum of 1000 mg was given per week as per package inserts, and if a second infusion was necessary, this was planned at least 1 week apart. The first infusion consisted of 1000 mg and the second infusion the remainder of the dose. Intravenous iron was given in a short-stay setting or colon care unit and infused over 15 min under supervision of a physician or registered nurse. Patients who received the oral iron treatment received three 200 mg ferrous fumarate tablets daily from randomisation until the day before surgery, and patients were asked about medication adherence at admission. The planned surgery was not postponed for intravenous or oral iron treatment. When patients were randomly assigned to receive oral iron

remained anaemic after surgery, the oral iron treatment was continued.

Clinical outcome data were collected preoperatively, during admission, and at 30 days and at 6 months postoperatively. Patients received health-related quality of life and fatigue questionnaires (EQ-5D, EORTC-C30, EORTC CR29, the iMTA Medical Consumption Questionnaire, and the iMTA Productivity Cost Questionnaire at baseline, 4 weeks, and 6 months, and Brief Fatigue Inventory at baseline, admission, 2 weeks, 4 weeks, 3 months, and 6 months). Blood samples to assess haemoglobin and iron values were taken at baseline, admission, and at day 1 and 7 postoperatively, and after 1, 2, and 3 months. All measurements were done by local laboratories. All serious adverse events that were possibly related to the protocol treatment were reported to the coordinating investigator within 24 h and reported to the regulatory authorities. All other adverse events were recorded in the case report form. Adverse events were classified as Common Terminology Criteria for Adverse Events (version 5).

Outcomes

The primary outcome of this study was the proportion of patients whose haemoglobin level normalised (≥7·5 mmol/L [12 g/dL] for women and ≥8 mmol/L [13 g/dL] for men) from the beginning of treatment to surgery. Secondary outcomes included morbidity (assessed with the Clavien-Dindo classification and the Comprehensive Complication Index [CCI]), reintervention rate, number of blood transfusions needed, total number of readmissions, length of hospital stay, admissions to intensive care units (ICUs), absolute change in haemoglobin from baseline before surgery and postoperatively, time needed to reach normalisation of haemoglobin level, change in baseline of other iron or haematological parameters (ie, transferrin saturation, ferritin, and C-reactive protein), and health-related quality of life and fatigue scores. Cutoffs for normal iron stores were defined as above normal local value (ferritin >800 µg/L or transferrin saturation >20%).

Statistical analysis

For a reasonable calculation of the required sample size, a dichotomous outcome was chosen as a primary endpoint. The trial was designed as a superiority trial, hypothesising that a greater percentage of patients would reach a normalised haemoglobin level with intravenous, rather than oral, iron supplementation. The calculation was based on a previous RCT comparing intravenous and oral iron supplementation in post-partum women with iron deficiency anaemia.[14] After 2 weeks of treatment, normalisation of haemoglobin was seen in 55% of the intravenous group and 35% of the oral group. A somewhat lower rate of normalisation of haemoglobin would be expected in patients with colorectal cancer compared with post-partum women, and therefore, the percentage of

	Total (n=202)	Intravenous iron (n=96)	Oral iron (n=106)
Sex			
Men	105 (52%)	49 (51%)	56 (53%)
Women	97 (48%)	47 (49%)	50 (47%)
Age, years	71 (62–80)	72 (63–79)	70 (61–81)
BMI, kg/m²	26 (5); n=192	27 (6); n=92	26 (5); n=100
American Society for Anesthesiology score			
1	44 (22%)	20 (21%)	24 (23%)
2	107 (53%)	54 (56%)	53 (50%)
3	51 (25%)	22 (23%)	29 (27%)
Smoker			
Current	25/198 (13%)	15/96 (16%)	10/102 (10%)
Former	54/198 (27%)	28/96 (29%)	26/102 (25%)
Never	119/198 (60%)	53/96 (55%)	66/102 (65%)
Tumour location			
Colon ascendens	74 (37%)	36 (38%)	38 (36%)
Caecum	41 (20%)	22 (23%)	19 (18%)
Sigmoid	26 (13%)	15 (16%)	11 (10%)
Colon transversum	19 (9%)	11 (11%)	8 (8%)
Flexura hepatica	15 (7%)	3 (3%)	12 (11%)
Colon descendens	14 (7%)	5 (5%)	9 (8%)
Rectum	10 (5%)	3 (3%)	7 (7%)
Flexura lienalis	3 (1%)	1 (1%)	2 (2%)
Tumour stage			
TX	17/188 (9%)	11/90 (12%)	6/98 (6%)
T1	7/188 (4%)	4/90 (4%)	3/98 (3%)
T2	37/188 (20%)	17/90 (19%)	20/98 (20%)
T3	107/188 (57%)	51/90 (57%)	56/98 (57%)
T4	20/188 (11%)	7/90 (8%)	13/98 (13%)
Node stage			
NX	23/186 (12%)	12/90 (13%)	11/96 (12%)
N0	95/186 (51%)	47/90 (52%)	48/96 (50%)
N1	56/186 (30%)	22/90 (24%)	34/96 (35%)
N2	12/186 (6%)	9/90 (10%)	3/96 (3%)
Metastasis stage			
M0	0	0	0
Preoperative radiotherapy	0	0	0
Previous blood transfusion	6 (3%)	3 (3%)	3 (3%)
History of cardiac disease	42 (21%)	19 (20%)	23 (22%)
Anticoagulant medication use	53 (26%)	23 (24%)	30 (28%)
Treatment type			
Intravenous	97 (48%)	95 (99%)	2 (2%)
Oral	105 (52%)	1 (1%)	104 (98%)
Median interval from randomisation to intervention, days	1 (0–5); n=196	5 (2–7); n=95	0 (0–1); n=101
Median interval from intervention to surgery, days	17 (12–24); n=198	14 (11–22); n=94	19 (13–27); n=104
Surgery approach			
Open	18 (9%)	10 (10%)	8 (8%)
Laparoscopic	184 (91%)	86 (90%)	98 (92%)
Conversion	21/183 (11%)	7/85 (8%)	14/98 (14%)

(Table 1 continues on next page)

	Total (n=202)	Intravenous iron (n=96)	Oral iron (n=106)
(Continued from previous page)			
Operation type			
Right hemicolectomy	136 (67%)	64 (67%)	72 (68%)
Transversum resection	1 (<1%)	0	1 (1%)
Left hemicolectomy	28 (14%)	14 (15%)	14 (13%)
Subtotal colectomy	4 (2%)	2 (2%)	2 (2%)
Low anterior resection	22 (11%)	11 (11%)	11 (10%)
Abdomino–perineal resection	1 (<1%)	0	1 (1%)
Sigmoid resection	4 (2%)	3 (3%)	1 (1%)
Partial mesorectal excision	3 (2%)	2 (2%)	1 (1%)
Other*	1 (<1%)	0	1 (1%)

Data are n (%), n/N (%), mean (SD), or median (IQR). NA=not available. *In one patient, the tumour could not be resected because of ingrowth in surrounding tissues and a diverting stoma was created.

Table 1: **Baseline, treatment, and surgical characteristics**

patients expected to reach normalised haemoglobin (≥7·5 mmol/L [12 g/dL] for women and ≥8 mmol/L [13 g/dL] for men) was 45% in the intravenous iron group and 25% in the oral iron group. On the basis of these proportions, a sample size of 89 patients per group was needed for a χ^2 test to achieve 80% power at a two-sided α of 0·05. With an estimated loss to follow-up of 10%, a sample size of 198 was calculated. After the inclusion of 152 patients, the actual loss to follow-up rate for the primary endpoint was 23% (35 of 152). At the beginning of the study, blood samples on the day of admission were not taken from several patients. The number of patients affected appeared to be similar for both groups and was mainly due to logistical issues, such as earlier rescheduling of the resection without notification of the study team. After adjustment, a sample size of 220 patients was recalculated. nQuery Advisor (version 7.0) was used to calculate the sample size.

For more on **OpenClinica** see https://www.openclinica.com/

Data were collected by local study personnel in a secure web-based case report form system (OpenClinica). Patients were included in the intention-to-treat analysis if they received the first dose of study medication. The primary outcome and dichotomous outcomes were calculated using a two-sided χ^2 test at a significance level of 0·05 and presented with relative risk (RR) ratios and 95% CIs. If the observed count was less than 10, a Fisher's exact test was used for the dichotomous outcomes. Depending on distribution, continuous outcomes were reported by means and standard deviations, analysed with a Student's *t* test and presented with a mean difference and 95% CIs or reported by medians and interquartile ranges and analysed using the Mann–Whitney U test. An as-treated analysis was done on patients that received the allocated treatment in the correct dose, with the first dose at least 2 weeks before surgery. A subgroup analysis was done for the following factors used for stratification in the randomisation process: aged 70 years or younger, aged older than 70 years, baseline haemoglobin 6·2 mmol/L (10 g/dL) or less, baseline haemoglobin more than 6·2 mmol/L (10 g/dL), and sex. For the continuous quality of life outcomes, a linear mixed model was used with autoregressive structure and time, and the baseline score and randomisation results were used as fixed effects. A Bonferroni correction was used to correct for multiple testing. Patients with missing data were excluded from analysis. Available patients with complete data were reported per outcome. Statistical analysis was done with SPSS Statistics, version 26.0.

A data safety monitoring board was instituted to guard the safety of included patients, give advice on the continuation of the study upon superiority of one of the types of treatment, and guard the methodological quality of the study. The data safety monitoring board did the interim analyses to ensure these goals. The study was monitored independently by a clinical research unit as described in a monitoring plan to ensure quality and adherence to the protocol. During the first COVID-19 wave in 2020, the trial was halted for 3 months to ensure safety of patients and study personnel and resulted in a slightly decreased inclusion rate afterwards. The trial was registered at ClinicalTrials.gov, NCT02243735.

Role of the funding source

The funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

Results

Between Oct 31, 2014, and Feb 23, 2021, a total of 220 patients were included in the study, of whom 110 were randomly assigned to intravenous iron and 110 to oral iron treatment. 14 patients were excluded from the intravenous iron group after randomisation and four were excluded from the oral iron group (figure 1). In the intravenous iron group, 95 (99%) of 96 patients received the allocated treatment, and one patient crossed over to the oral iron treatment because of personal preference. In the oral iron group, 104 (98%) of 106 patients received the allocated treatment, and two patients crossed over to the intravenous iron treatment.

Baseline characteristics among the treatment groups were comparable (table 1). The median age was 71 years (IQR 62–80) and 105 (52%) of 202 patients were men. Mean BMI was 26 kg/m² (SD 5), and most patients had tumours in the ascending colon (74 [37%] of 202) or caecum (41 [20%] of 202). According to the American Society for Anesthesiology classification, 44 (22%) of 202 patients were scored 1, 107 (53%) were scored 2, and 51 (25%) were scored 3. Anticoagulant medication was used by 53 (26%) patients, and six (3%) patients had received a previous blood transfusion. Baseline albumin levels were the same in both groups (38 g/L *vs* 38 g/L).

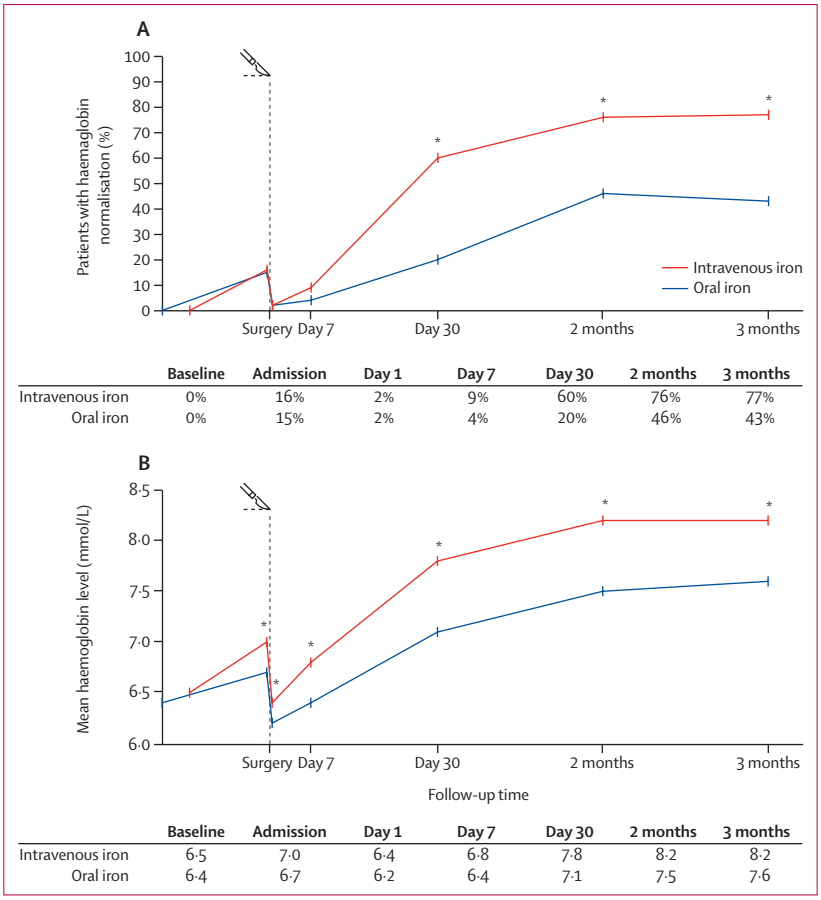
The median interval from randomisation to intervention with iron supplementation was 5 days (IQR 2–7) in the

intravenous iron group and 0 days (IQR 0–1) in the oral iron group (p<0·0001). The median interval from intervention to surgery was 14 days (IQR 11–22) in the intravenous iron group and 19 days (IQR 13–27) in the oral iron group (p=0·0064). The most prevalent treatment-related adverse event was discoloured faeces (grade 1) after oral iron treatment (14 [13%] of 105), and no treatment-related serious adverse events or deaths were observed in either group. Most patients (136 [67%] of 202) had a right hemicolectomy, and the type of surgery was similar in both groups (table 1; appendix pp 5–6).

Haemoglobin levels were similar at randomisation for intravenous iron (mean 6·5 mmol/L [SD 10·5 g/dL]) and oral iron (haemoglobin 6·4 mmol/L [10·3 g/dL], p=0·48), and were higher at day of admission in the intravenous iron group (7·0 mmol/L [11·3 g/dl] *vs* 6·7 mmol/L [10·8 g/dL], p=0·041) compared with the oral iron group. Mean absolute change in haemoglobin from baseline until admission was similar after intravenous iron compared with oral iron (0·53 mmol/L [0·85 g/dl] *vs* 0·36 mmol/L [0·58 g/dL]; p=0·13). The number of patients with complete normalisation of haemoglobin at day of admission was low and did not differ between the intravenous iron and oral iron groups at admission (14 [17%] of 84 *vs* 15 [16%] of 97; RR 1·08 [95% CI 0·55–2·10]; p=0·83), or in the first postoperative days.

The proportion of patients with a normalised haemoglobin level was significantly greater in the intravenous group than the oral iron group at 30 days (49 [60%] of 82 *vs* 18 [21%] of 88; RR 2·92 [95% CI 1·87–4·58]; p<0·0001), 2 months (56 [76%] of 74 *vs* 37 [45%] of 83; RR 1·69 [95% CI 1·29–2·23]; p<0·0001), and 3 months (56 [76%] of 74 *vs* 37 [43%] of 86; RR 1·76 [95% CI 1·34–2·32]; p<0·0001) follow-up (figure 2). Serum transferrin saturation, ferritin and haematocrit levels were similar at baseline, but were significantly higher in the intravenous iron group at day of admission and most postoperative timepoints (figure 3; appendix pp 3, 7–8).

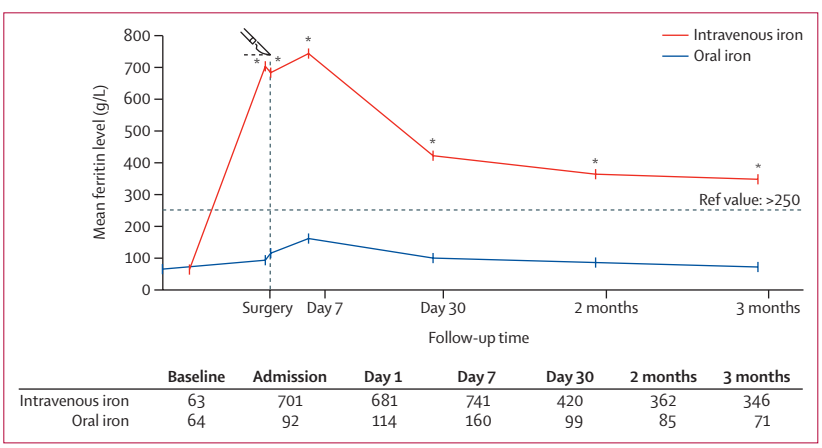
The postoperative cumulative complication rate at 6 months was 46 (48%) of 96 patients in the intravenous iron group and 60 (57%) of 106 in the oral group, and complications at Clavien–Dindo score of 3 or higher were seen in 12 (13%) of 96 patients in the intravenous iron group versus 18 (17%) of 106 in the oral iron group (table 2). The intravenous iron group showed no statistically significant difference in the CCI score (12·5 [SD 19] *vs* 17·5 [SD 24]; p=0·10) and numbers of patients who received reinterventions (8 [8%] of 96 *vs* 17 [16%] of 106, RR 0·52 [95% CI 0·24–1·15]; p=0·13), compared with the oral iron group. During surgery, 2 (2%) of 202 patients received a blood transfusion in the entire cohort, whereas 9 (9%) of 96 patients in the intravenous group received a blood transfusion during follow-up at 6 months compared with 15 (14%) of 106 in the oral iron group (RR 0·66 [95% CI 0·30–1·44]; p=0·39).



	Baseline	Admission	Day 1	Day 7	Day 30	2 months	3 months
Intravenous iron	0%	16%	2%	9%	60%	76%	77%
Oral iron	0%	15%	2%	4%	20%	46%	43%

	Baseline	Admission	Day 1	Day 7	Day 30	2 months	3 months
Intravenous iron	6·5	7·0	6·4	6·8	7·8	8·2	8·2
Oral iron	6·4	6·7	6·2	6·4	7·1	7·5	7·6

Figure 2: **Haemoglobin normalisation**
(A) Percentage of patients with haemoglobin normalisation. (B) Haemoglobin levels (mmol/L) during follow-up. *The differences found were statistically significant.



	Baseline	Admission	Day 1	Day 7	Day 30	2 months	3 months
Intravenous iron	63	701	681	741	420	362	346
Oral iron	64	92	114	160	99	85	71

Figure 3: **Ferritin levels (µg/L) during follow-up**
*The differences found were statistically significant.

The proportion of patients readmitted was similar for the intravenous iron and oral iron groups (10 [10%] of 96 *vs* 10 [9%] of 106; RR 1·10 [95% CI 0·48–2·54]; p=0·82), and there was no difference in the total length of stay between intravenous iron and oral iron (5 days [IQR 4–9] *vs* 5 days [IQR 4–10]; p=0·55). Six (6%) of 96 patients in the

	Total (n=202)	Intravenous iron (n=96)	Oral iron (n=106)	Effect size (95% CI)	p value
Intraoperative complications	12 (6%)	7 (7%)	5 (5%)	1·55 (0·51–4·71)	0·55
Postoperative complications					
During admission	91 (45%)	38 (40%)	53 (50%)	0·79 (0·58–1·08)	0·14
30 days	101 (50%)	43 (45%)	58 (55%)	0·82 (0·62–1·09)	0·16
6 months	106 (52%)	46 (48%)	60 (57%)	0·85 (0·65–1·11)	0·22
Clavien-Dindo classification*					
I	46 (23%)	22 (23%)	24 (23%)	1·01 (0·61–1·68)	0·96
II	66 (33%)	26 (27%)	40 (38%)	0·72 (0·48–1·08)	0·11
IIIa	10 (5%)	4 (4%)	6 (6%)	0·74 (0·21–2·53)	0·75
IIIb	9 (4%)	3 (3%)	6 (6%)	0·55 (0·14–2·15)	0·50
IVa	3 (1%)	2 (2%)	1 (1%)	2·21 (0·20–23·97)	0·61
IVb	4 (2%)	1 (1%)	3 (3%)	0·37 (0·04–3·48)	0·62
V	7 (3%)	2 (2%)	5 (5%)	0·44 (0·09–2·22)	0·45
Clavien–Dindo score of 3 or higher*	30 (15%)	12 (13%)	18 (17%)	0·74 (0·37–1·45)	0·37
Glasgow prognostic score					
0 (good prognosis)	70/150 (47%)	36/72 (50%)	34/78 (44%)	1·15 (0·82–1·62)	0·43
1 (intermediate prognosis)	56/150 (37%)	27/72 (38%)	29/78 (37%)	1·01 (0·67–1·53)	0·97
2 (poor prognosis)	24/150 (16%)	9/72 (13%)	15/78 (19%)	0·65 (0·30–1·39)	0·26
Reintervention rate*					
During admission	16 (8%)	6 (6%)	10 (9%)	0·66 (0·25–1·75)	0·45
30 days	22 (11%)	7 (7%)	15 (14%)	0·52 (0·22–1·21)	0·17
6 months	25 (12%)	8 (8%)	17 (16%)	0·52 (0·24–1·15)	0·13
Reintervention type*					
Surgical, during admission	11 (5%)	3 (3%)	8 (8%)	0·41 (0·11–1·52)	0·22
30 days	12 (6%)	3 (3%)	9 (8%)	0·37 (0·10–1·32)	0·14
6 months	12 (6%)	3 (3%)	9 (8%)	0·37 (0·10–1·32)	0·14
Endoscopic, admission	2 (1%)	0	2 (2%)	NA	0·50
30 days	2 (1%)	0	2 (2%)	NA	0·50
6 months	3 (1%)	0	3 (3%)	NA	0·25
Radiological, admission	5 (2%)	4 (4%)	1 (1%)	4·42 (0·50–38·8)	0·19
30 days	10 (5%)	5 (5%)	5 (5%)	1·10 (0·33–3·70)	1·00
6 months	12 (6%)	6 (6%)	6 (6%)	1·10 (0·37–3·31)	1·00
Blood transfusions					
Peroperative	2 (1%)	1 (1%)	1 (1%)	1·10 (0·07–17·41)	1·00
During admission	20 (10%)	7 (7%)	13 (12%)	0·60 (0·25–1·43)	0·35
30 days	23 (11%)	8 (8%)	15 (14%)	0·59 (0·26–1·33)	0·27
6 months	24 (12%)	9 (9%)	15 (14%)	0·66 (0·30–1·44)	0·39

(Table 2 continues on next page)

intravenous iron group and 12 (11%) of 106 in the oral iron group were admitted to ICUs (RR 0·55 [95% CI 0·22–1·41]; p=0·23), and the mortality rate was 2 (2%) of 96 patients in the intravenous iron group and 7 (7%) of 106 in the oral iron group (RR 0·32 [95% CI 0·07–1·48]; p=0·18). No differences in treatment-emergent serious adverse events were seen (table 3). Serious adverse events reported were anastomotic leakage (n=11), aspiration pneumonia (n=5), intra-abdominal abscess (n=5), myocardial infarction (n=2), omental ischaemia (n=1), internal herniation (n=1), duodenal perforation (n=1), postoperative bleeding (n=1), cauda equina syndrome (n=1), pneumonia (n=1), fascial dehiscence (n=1), congestive heart failure (n=1), and intestinal perforation (n=1).

The as-treated analysis comprised 125 (62%) of 202 patients (appendix p 9). Patients were excluded from the as-treated analysis because they crossed between treatment groups (n=3), received the wrong or incomplete intravenous dose (n=20), reported multiple missed oral doses (n=2), or there was less than 2 weeks between the intervention beginning and surgery (n=52). In the as-treated analysis, there was both a lower overall reintervention rate in the intravenous iron group compared with the oral iron group (3 [6%] of 51 *vs* 13 [18%] of 74; RR 0·34 [95% CI 0·10–1·12]; p=0·062) and a lower surgical reintervention rate (0 [0%] of 51 *vs* 8 [11%] of 74; p=0·021). All other outcomes had similar results across groups, even though there was a greater

	Total (n=202)	Intravenous iron (n=96)	Oral iron (n=106)	Effect size (95% CI)	p value
(Continued from previous page)					
Adjuvant treatment	61/202 (30%)	31/96 (32%)	30/106 (28%)	1·14 (0·75–1·74)	0·54
Adjuvant chemotherapy	60/181 (33%)	31/89 (35%)	29/92 (32%)	1·11 (0·73–1·67)	0·64
Additional oncological surgery†	5/202 (3%)	0	5 (5%)	NA	0·061
Readmissions					
30 days	11 (5%)	4 (4%)	7 (7%)	0·60 (0·18–1·97)	0·54
6 months	20 (10%)	10 (10%)	10 (9%)	1·10 (0·48–2·54)	0·82
Intensive care unit admission	18 (9%)	6 (6%)	12 (11%)	0·55 (0·22–1·41)	0·23
Length of stay, days	5 (4–10); n=202	5 (4–9)	5 (4–10)	NA	0·55
Index admission	5 (4–8); n=201	5 (4–9)	5 (4–9)	NA	0·55
Readmissions	0 (0–0); n=202	0 (0–0)	0 (0–0)	NA	0·75
Stay per readmission	7 (3–20); n=20	7 (5–32)	5 (2–17)	NA	0·18
Mortality	9 (4%)	2 (2%)	7 (7%)	0·32 (0·07–1·48)	0·18
Oncological	2 (1%)	0	2 (2%)	NA	0·50
Treatment-related adverse events	31 (15%)	8 (8%)	23 (22%)	0·38 (0·18–0·82)	0·0085
Grade 3 or higher	0	0	0	NA	NA
Serious adverse events	30 (15%)	12 (13%)	18 (17%)	0·74 (0·37–1·45)	0·37
Comprehensive Complication Index score	15·1 (22); n=202	12·5 (19)	17·5 (24)	−4·98 (10·98–1·03)	0·10

Data are n (%), n/N (%), mean (SD), or median (IQR). NA=not available. *Reintervention for further oncological treatment was not used in this analysis. †These surgeries consisted of hyperthermic intraperitoneal chemotherapy (n=3), decompression laminectomy for vertebral metastasis (n=1), and resection for pancreatic cancer (n=1).

Table 2: **Surgical outcomes**

absolute difference in haemoglobin levels during follow-up, with higher levels in the intravenous iron group.

Patients with a baseline haemoglobin of more than 6·2 mmol/L (10·0 g/dL) had better outcomes after treatment with intravenous iron than oral iron (appendix pp 4, 11). At 6 months, the cumulative reintervention rate was lower in the intravenous iron group (1 [2%] of 62 *vs* 11 [18%] of 61; RR 0·09 [95% CI 0·01–0·67]; p=0·0022), as was the surgical reintervention rate (0 [0%] of 62 *vs* 5 [8%] of 61; p=0·028) and the ICU admission rate (1 [2%] of 62 *vs* 8 [13%] of 61; RR 0·12 [95% CI 0·02–0·95]; p=0·017). Comparable numbers of complications with Clavien–Dindo score 3 and a CCI score were observed between groups. Patients with a baseline haemoglobin level of 6·2 mmol/L (10·0 g/dL) or less had similar results to the main analysis.

Male patients appeared to benefit more from intravenous iron compared with oral iron, with a lower number of Clavien–Dindo score 3 or higher complications, lower CCI score, lower reintervention rate at 6 months, and lower rate of ICU admissions. In female patients and other subgroup analyses, results were similar to the main analysis (appendix pp 10, 12–14).

The linear mixed model revealed no differences in Brief Fatigue Inventory scores between groups (p=0·36), using time, baseline score, and randomisation results as fixed effects. Similar results were seen for the EQ5D index value (p=0·46) and EQ5D health status score (p=0·46). For the EORTC-30, improved results were observed in the oral iron group on the Role Functioning Scale (p=0·031). Similarly, for the EORTC-C29, the oral iron group had better results on three symptom scales than the intravenous iron group: weight (p=0·0040), increased stool frequency (p=0·018), and dyspareunia (p=0·020; appendix pp 15–17).

Discussion

This international RCT investigating the efficacy of intravenous versus oral iron treatment for preoperative iron deficiency anaemia in patients undergoing surgery for colorectal cancer did not reveal a superiority of intravenous over oral iron treatment with respect to haemoglobin-normalisation on the day of admission. However, intravenous iron treatment showed improved haemoglobin normalisation after surgery compared with oral iron treatment. Serum transferrin saturation, ferritin, and haematocrit levels were all significantly higher in the intravenous iron group at day of admission and most postoperative timepoints. By contrast, oral iron treatment did not restore ferritin levels at any timepoint included in this study.

To our knowledge, this is the first RCT to report findings on the efficacy of preoperative iron supplementation for patients with colorectal cancer on relevant clinical outcomes, such as complications, reinterventions, and postoperative stay, to provide evidence on whether intravenous iron or oral iron supplementation has an effect in prehabilitation for patients undergoing colorectal surgery.

This RCT showed that the proportion of patients with normalised haemoglobin on the day of surgery was small in both treatment groups. A possible explanation is that

	Intravenous iron (n=96)				Oral iron (n=106)			
	Grade 1–2	Grade 3	Grade 4	Grade 5	Grade 1–2	Grade 3	Grade 4	Grade 5
Discoloured faeces	0	0	0	0	14 (13%)	0	0	0
Anastomotic leakage	0	5 (5%)	0	0	0	3 (3%)	2 (2%)	1 (1%)
Aspiration pneumonia	0	0	1 (1%)	1 (1%)	0	0	0	3 (3%)
Intra-abdominal abscess	0	1 (1%)	0	0	0	4 (4%)	0	0
Omental ischemia	0	1 (1%)	0	0	0	0	0	0
Myocardial infarction	0	0	1 (1%)	0	0	1 (1%)	0	0
Postoperative bleeding	..	..	..	..	0	1 (1%)	1 (1%)	0
Internal herniation	0	0	1 (1%)	0	0	0	0	0
Duodenal perforation	0	0	0	1 (1%)	0	0	0	0
Cauda equina syndrome*	0	0	0	0	0	1 (1%)	0	0
Pneumonia	0	0	0	0	0	1 (1%)	0	0
Fascial dehiscence	0	0	0	0	0	1 (1%)	0	0
Congestive heart failure	0	0	0	0	0	0	1 (1%)	0
Intestinal perforation	0	0	0	0	0	0	0	1 (1%)

Grade 1–2 treatment-emergent adverse events occurring in more than 10% of patients and all grade 3–5 events are reported. *One patient developed cauda equine syndrome during admission caused by a previously unknown vertebral metastasis, requiring emergency surgery.

Table 3: **Treatment-emergent adverse events**

the median time from intravenous iron supplementation to surgery was too short, as over half the patients underwent surgery within 2 weeks of the first intravenous iron supplementation. Notably, surgery in this study was not postponed, as the effect of postponement was unclear and to reflect implementation in daily practice. Therefore, this short interval reflects clinical practice, because the time interval itself was no reason for exclusion from the study. Haemoglobin normalisation during follow-up were also lower than expected in our sample size calculation. The study used in our power calculation included postpartum women with iron deficiency anaemia and might not be ideally suitable, but was chosen because no other RCT comparing intravenous and oral iron was available at the time.[14]

The results from this study are in line with those from a 2020 RCT,[16] which also reported low proportions of patients with haemoglobin normalisation by the day of surgery. The study compared intravenous iron supplementation with placebo in patients undergoing major abdominal surgery for several indications, and the preoperative haemoglobin-normalisation was reportedly 21% after intravenous iron and 10% after placebo (RR 2·06 [92% CI 1·27–3·35]) after 2 weeks of treatment.[16]

Although complete haemoglobin normalisation was not reached on the day of surgery in any group, our results clearly showed differences between the treatment regimens during the convalescent phase. Almost two-thirds of patients who received intravenous iron reached haemoglobin-normalisation 6 weeks after infusion. If haemoglobin normalisation itself is considered important, then this period of delay to surgery should be considered in future. The greatest increase in the proportion of patients who reached haemoglobin-normalisation occurred at 4 weeks after surgery; thus, a postponement of surgery of this length to prepare patients could be considered. Even though surgery can usually be facilitated within 2 weeks in the Netherlands, delaying surgery for at least 4 weeks to give the patient iron treatment appears to be safe.[21] Nevertheless, even without reaching normalised haemoglobin, the restoration of iron reserves using intravenous iron treatment showed a positive effect on postoperative complications.

Oral iron supplementation was unable to restore ferritin levels at any time during follow-up. Treatment with oral iron might seem attractive due to its simplicity and low cost, but it might not be the optimal treatment for patients with colorectal cancer.[7] During inflammatory conditions, iron absorption from the gut is hampered, and iron released from cells is inhibited and hence not available for metabolisation.[22,23] Additionally, adherence to oral iron treatment can be impaired in patients with colorectal cancer. Digestion problems and possible obstructive complaints caused by the tumour might lead to a reduced intake of oral iron below the dosage prescribed. Our data suggest that oral iron in patients with colorectal cancer is unable to restore iron storage levels. Apparently, all orally supplemented iron that was absorbed was used for erythropoiesis, as reflected by the increase in haemoglobin levels when iron reserves remained depleted.

Transferrin saturation was chosen over ferritin as an inclusion criterium in this study, because ferritin can also be elevated by inflammation by being an acute phase protein. A potential effect of inflammation causing anaemia might have been possible in this study, but we expect this effect was small. Both transferrin saturation and ferritin were low at baseline.

Patients with mild anaemia who were treated with intravenous iron showed better clinical outcomes than those treated with oral iron. This is of particular interest because this subgroup of patients often remains untreated for anaemia. Although haemoglobin levels were not different on the day of admission or on the day after surgery, fewer ICU admissions and reinterventions were reported in patients who underwent intravenous iron treatment. It is possible that the increased iron reserves (as seen in the increased ferritin levels) ameliorated metabolic reactions that rely on iron. Low ferritin levels might be a more relevant biomarker for worse clinical outcomes than previously thought. The results from this RCT suggest that the restoration of iron reserves is more relevant than the restoration of the haemoglobin level.

No differences were seen in functional outcomes between the intravenous and oral iron treatment groups, despite the improved haemoglobin-normalisation after intravenous-iron treatment. A third of patients had adjuvant chemotherapy, which might have mitigated the

effect of improved haemoglobin levels. Furthermore, it is possible that the questionnaires used in this study were unable to detect a difference reflecting the improved haemoglobin levels in the intravenous iron group. A study investigating the effects of iron treatment in patients with heart failure found a significantly greater 6 min walking distance after intravenous iron treatment compared with oral iron treatment.[24]

There were no differences observed in the proportions of patients receiving blood transfusions between patients treated with intravenous and oral iron, and they were relatively low in both groups (intravenous [9%] *vs* oral [14%]). We expected this to be low and inadequate as a primary endpoint, because an RCT[16] found no difference in allogeneic blood transfusion rate during follow-up when comparing intravenous iron treatment and placebo. A review of six RCTs that investigated some form of iron treatment for preoperative anaemia found no difference in blood transfusion rates when comparing iron therapy with placebo or standard care.[15] The transfusion rate in colorectal surgery is generally too low to consider the need for transfusion as a suitable primary endpoint when studying iron supplementation in these patients.

In this study we have documented the short-term outcomes of different iron treatments on patients, but the long-term oncological outcomes are still awaited. Iron treatment might impair oncological outcomes, because increased concentrations of intraluminal iron could promote the growth of pathogenic gut bacteria involved in tumour progression.[25] However, whether or not iron supplementation is associated with tumour recurrence is yet to be determined.

Over the past two decades, many improvements have been made to surgical care for patients with colorectal cancer, resulting in improved oncological outcomes. In the past 5 years, there has been greater focus on the prehabilitation of patients to ensure that they are fit for surgery, with measures including home physical therapy training plans, high protein diets, smoking cessation, and weight loss programmes.[26] Intravenous iron is a relatively straightforward intervention that requires one or two visits, can be carried out in an outpatient setting, and is not strenuous for the patient. Therefore, the intervention should be considered as one easy intervention within a prehabilitation programme. Logistics can be optimised by administering the intravenous iron shortly after the haemoglobin and ferritin levels are known, and treatment would ideally start directly after the patient is informed about undergoing surgery. As shown in our study, intravenous iron treatment was feasible across centres, administered within 5 days following diagnosis of iron deficiency with a very low number of adverse events during supplementation. Additionally, haemoglobin could be a potential frailty marker to identify those patients that are in need of prehabilitation, because it reflects tumour progression, nutritional status, and functional status.

One of the strengths of this study was the pragmatic setup and its generalisability. It is the first study that clearly selected patients undergoing surgery for colorectal cancer with a proven preoperative iron deficiency anaemia with clinically significant endpoints. No previous studies are available with such a large number of patients with colorectal cancer receiving maximal doses of iron treatment.

One possible limitation of this study was that the sample size needed to be recalculated, because of incomplete primary endpoint data. However, this limitation appeared to affect both treatment groups similarly and was mainly due to logistical issues, such as earlier rescheduling of the resection without the study team receiving a notification. We do not believe this limitation has influenced the results between groups. A related limitation might be that some patients received an incomplete or wrong dose of intravenous iron, which was mostly caused by earlier rescheduling of surgery. Another limitation was the dosing schedule of oral iron in our study. New evidence suggests that lower dosage regimens on intermittent days, instead of daily dosage, might increase uptake of oral iron and reduce side-effects, while increasing haemoglobin levels.[27] Another possible limitation is that our study was possibly underpowered to detect statistical differences in clinical outcomes in the entire cohort, as could be seen in the lower absolute rates in complications, reinterventions, ICU admissions, and mortality after intravenous iron treatment.

Restoration of iron stores is only feasible with intravenous iron, justifying intravenous iron infusion as part of a prehabilitation programme for patients undergoing colorectal surgery to reduce postoperative negative sequelae. In selected patients, surgery might be delayed to augment the effect of intravenous iron on haemoglobin normalisation.

FIT collaborative group

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Contributors

WAAB, CJB, KMAJT, MLD, and WAB were involved in study conception and design. WAAB and WAB obtained funding. KT, WAB, SXR, ERJB, CJB, RH, KMAJT, JBT, ECJC, GH, TK, AAWvG, GJV, JABvdH, CS, AS, AWHvdV, ESvdZ, MW, HLvW, and WAB implemented the study. KT, WAAB, ERJB, and SXR were involved in data curation. CJB, MLD, and WAB were involved as methodologist. MLD was involved as statistician. KT, WAAB, MLD, and WAB were involved in the analysis. KT, WAAB, CJB, RH, NPJ, and WAB were involved in interpreting the data. KT and WAB wrote the first draft of the manuscript. All authors read and approved the manuscript. KT, WAAB, SXR, ERJB, and WAB have access to the raw data. All authors had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Declaration of interests

WAB received funding from Vifor Pharma for this trial. All other authors declare no competing interests.

Data sharing

Data collected in this study will not be made publicly available, but will be available upon reasonable request to the authors via email. Other research material (detailed protocol, informed consent forms) will be directly available after publication on request to the authors.

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