Original article

Single-dose intravenous ferric carboxymaltose infusion *versus* multiple fractionated doses of intravenous iron sucrose in the treatment of post-operative anaemia in colorectal cancer patients: a randomised controlled trial

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Background - Recent clinical guidelines suggest that treatment of postoperative anaemia in colorectal cancer surgery with intravenous iron reduces transfusion requirements and improves outcomes. The study aimed at comparing two intravenous iron regimens in anaemic patients after colorectal cancer surgery.

Materials and methods - This was a single-centre, open-label, randomised, controlled trial in patients undergoing elective colorectal cancer surgery. Patients with moderate to severe anaemia (haemoglobin [Hb] <11 g/dL) after surgery were randomly assigned 1:1 to receive ferric carboxymaltose (FC; 1,000 mg, single dose) or iron sucrose (IS; 200 mg every 48 hours until covering the total iron deficit or discharge). Randomisation was stratified by Hb level: <10 g/dL (Group A) or ≥10–10.9 (Group B). The primary endpoint was the change in Hb concentration at postoperative day 30. Secondary endpoints included iron status parameters, transfusion requirements, complications, and length of hospital stay.

Results - From September 2015 to May 2018, 104 patients were randomised (FC 50, IS 54). The median intravenous iron dose was 1,000 mg and 600 mg in the FC and IS groups, respectively. There were no between-group differences in mean change in Hb from postoperative day 1 to postoperative day 30 (FC: 2.5 g/dL, 95% CI: 2.1-2.9; IS: 2.4 g/dL, 95% CI: 2.0-2.8; p=0.52), in transfusion requirements or length of stay. The infection rate was lower in the FC group compared with the IS group (9.8% *vs* 37.2%, respectively).

Discussion - The administration of approximately 500 mg of IS resulted in an increase in Hb at postoperative day 30 similar to that of 1,000 mg of FC, but it was associated with a higher infection rate. Future research will be needed to confirm the results, and to choose the best regime in terms of effectiveness and side effects to treat postoperative anaemia in colorectal cancer patients.

Keywords: *postoperative anaemia, colorectal cancer, intravenous iron.*

Arrived: 18 May 2021
Revision accepted: 24 August 2021
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INTRODUCTION

Patients with colorectal cancer (CRC) often present associated anaemia, mainly attributed to iron deficiency due to blood loss and to the inflammation associated with neoplasia[1].

Blood Transfus 2022; 20: 310-318 DOI 10.2450/2021.0157-21
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Anaemia is aggravated in patients undergoing CRC surgery due to blood loss during the procedure[2,3].

Anaemia in the perioperative period increases morbidity and mortality[2-4]. It has been associated with adverse postoperative outcomes such as longer hospital stay, postoperative complications[2,4], and a higher risk of allogeneic blood transfusions[5,6]. On the other hand, transfusions are associated with increased postoperative infections, a higher rate of tumour recurrences, and higher 5-year mortality[2,4,7-9].

Clinical guidelines recommend intravenous iron (IVI) supplementation before and after surgery to reduce transfusion requirements[6]. The effects of treating preoperative anaemia have been widely studied[5,9-12], although there is no robust evidence for postoperative anaemia in patients undergoing colorectal cancer surgery[13-15].

There are two pharmacological options available in our hospital, in the context of a clinical protocol for optimisation of perioperative anaemia in CRC surgery: iron sucrose (IS), which is administered at doses of 200 mg every 48 hours (fractionated dose), and ferric carboxymaltose (FC) consisting of a single administration of 1,000 mg, which, mainly because of cost, is reserved for non-hospitalised patients.

An observational study in our hospital showed that 87% of patients undergoing surgery due to CRC had postoperative anaemia, while only 34% of them had received postoperative IVI, mostly IS. Importantly, it was observed that postoperative IVI administration to anaemic patients improved the recovery of Hb levels at 4 weeks after surgery with no increase in postoperative complications[16].

Besides issues about underuse of IVI, there was concern about the impact caused by changes in the clinical management of CRC surgery on site on the compliance of the full iron treatment schedule. Changes were based on the concept of "Enhanced Recovery After Surgery" (ERAS) or "fast-track surgery" and included early food intake and mobilisation aimed at achieving a prompt functional recovery and to eventually shorten the hospital stay[17]. Thus, those patients with early discharge were unable to receive all the scheduled IS doses and therefore did not receive the full iron dose according to their deficit, with potential clinical consequences.

Following these results, we identified the need for a randomised study aimed at providing convincing evidence of the benefits and risks of postoperative IVI therapy in subjects undergoing CRC surgery and to compare whether FC single-dose treatment had better results than fractionated IS in a setting of "fast -track surgery".

MATERIALS AND METHODS

Study design and participants

This is a single centre, open-label, randomised, controlled trial to compare the effectiveness of two different IVI regimens to treat postoperative anaemia in patients undergoing CRC surgery. The study was performed from September 2015 to May 2018 at the University Hospital Parc Taulí, Barcelona, Spain, a tertiary hospital. The study design has been published previously[18]. Briefly, eligible participants were individuals aged 18 years and over, who underwent elective CRC surgery. They were recruited at the scheduled preoperative hospital visit (4-6 weeks before the surgical intervention) during which the study was fully explained to them and, if they agreed to participate, they signed full informed consent. We excluded patients with a known history of iron allergy and pregnant women.

Randomisation and study interventions

On the first day after surgery (postoperative day 1, POD1), patients were screened for moderate-severe anaemia (Hb <11 g/dL). Patients with Hb levels ≥11 g/dL were not included in the study and followed the treatment schedule according to hospital protocols. We also excluded patients presenting surgical complications Clavien-Dindo[19] grade IV (life-threatening complications leading to transfer to the intensive care unit). Patients presenting with Hb <11 g/dL were randomly assigned 1:1 to receive either IV FC (FC group) or IS (IS group).

Randomisation was stratified according to Hb level at POD1: <10 g/dL (stratum A) or ≥10 - 10,9 g/dL (stratum B). Individual opaque sealed envelopes were created according to a randomisation list with consecutive numbers within each stratum; clinical investigators could not access the list. We used sealed envelopes to assign treatment to eligible patients by allocation of the lowest available number in the corresponding stratum on the POD1.

Procedures

FC (Ferinject®, Vifor Pharma España S.L, Barcelona, Spain) was given as open-label treatment on the day after

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surgery as a single 1,000 mg intravenous dose in a 15 min infusion. IS (Feriv; GES, Genéricos Españoles, Madrid, Spain) was also given as open-label repeated doses of 200 mg every 48 hours from POD1 up to hospital discharge or up to the total dose equivalent to the iron deficit, whichever occurred first. We calculated the total iron deficit with the Ganzoni Formula: Total Iron Deficit (mg) = 2.4 × patient's weight (kg) × (target Hb [13 g/dL] – current Hb [g/dL]) + 500 mg (iron stores), using data obtained prior to surgery. We registered iron stores status (ferritin [Ft] and transferrin saturation [TSAT]) at diagnosis of CRC and on admission, the day of surgery, and any preoperative Hb optimisation with IVI.

Hb level on admission and at 1, 4, and 30 days (POD1, POD 4, POD30) after surgery were recorded. Ft and TSAT % were obtained on hospital admission, the day of surgery, and POD30. We used a formula proposed by Brecher *et al.* to calculate intraoperative blood loss (erythrocyte loss = plasma volume × [preoperative haematocrit – day 5 haematocrit], where plasma volume is body surface × 2,530 for men and body surface × 2,430 for women). The formula was corrected in case of transfusion within 5 days before surgery (erythrocyte loss = plasma volume × [preoperative haematocrit – day 5 haematocrit] + transfused erythrocyte mass)[20].

The IVI dose received before discharge was collected, as well as the length of hospital stay (number of days of hospital admission from the day of surgery until date of discharge), use of blood products, and any postoperative complications. A special focus was given to the collection of data concerning infection, which was defined as fever with a requirement for intravenous antibiotics with or without a positive blood culture. Information concerning other adverse events was retrieved from the patient's medical records.

Study data were recorded on paper case report forms (CRF) specially designed for the study.

Outcomes

The primary endpoint of the study was the change in Hb levels from POD1 to POD30. We also studied the change from POD4 (nadir Hb) to POD30.

The secondary outcomes of the trial measured at POP30 were the percentage of patients with Hb ≥11 g/dL, ≥12 g/dL, and ≥13 g/dL (key secondary endpoint), Ft and TSAT values, transfusional rate and transfusional index, complications and length of hospital stay in both groups. Safety and tolerability were monitored throughout the study.

Statistical analysis

We based our sample size calculation on our existing data for patients undergoing CRC surgery with postoperative anaemia (published previously[16]) and targeted the same population with postoperative anaemia.

The hypothesis was that a difference of 0.75 g/dL would be observed in the change in Hb levels from POD1 to POD30 (primary endpoint) between the two studied regimens. With a two-sided risk of 5%, and a power of 80%, and, based on our previous observational data[16], assuming a common standard deviation of 1.3, a total of 48 evaluable patients per group needed to be included.

We defined two different populations of analysis: the Intention To Treat (ITT) population, consisting of all randomised patients with at least one Hb measurement after POD1 (for patients for whom Hb levels at POD30 were unavailable, the last value before POD30 was assigned) and the Per Protocol (PP) population which consisted of the ITT population who had Hb measurement at POD30, excluding patients who received a transfusion (considering that transfusion could be a relevant confounder on the main outcomes). The analysis of the primary endpoint was performed with the PP population.

Quantitative variables are described as means with standard deviations. Dichotomic variables are presented as absolute and relative frequencies.

Differences in the main variable (changes in Hb levels from POD1 to POD30) between the treatment groups were tested using an analysis of covariance (ANCOVA) using Hb at POD1 as a co-variable. χ^2 tests were used for the secondary variables. We performed a subgroup analysis for the stratification variable (Hb <10 g/dL and Hb ≥10 g/dL).

An exploratory multivariate analysis was performed to identify characteristics of patients associated with bigger changes in Hb levels and to identify subgroups of patients that may benefit most from the single IVI dose of FC.

Ethical considerations

This trial was conducted according to the principles of the Declaration of Helsinki and Good Clinical Practice Principles. The study protocol (version 2, April 2015) was approved by the Research Ethics Committee of University Hospital Parc Taulí in April 2015 and by the Spanish Medicines Agency (Agencia Española de Medicamentos

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y Productos Sanitarios) in July 2015. Written informed consent was obtained from each participant. The study was registered in the EU Clinical Trials Register (EudraCT: 2015-001005-13).

RESULTS

Between September 2015 and May 2018, 372 patients signed informed consent to participate. Of these, 268 were excluded either before or after surgery and were not randomised. Finally, 104 subjects were randomised to receive FC or IS. **Figure 1** shows the patients' characteristics and study groups, and the reasons for non-inclusion.

Baseline characteristics of patients at the time of surgery are shown in **Table I**.

At the time of CRC diagnosis, 82 (81.2%) presented anaemia (Hb <13 g/dL) and 12 (11.9%) had iron deficiency (ferritin <100 ng/mL and/or TSAT <20%) without anaemia. Mean Hb level at this time point was 11.2 g/dL (SD: 2.1). Most patients with anaemia had iron deficiency (70%). Information on iron stores at the time of diagnosis was not available for 27 patients.

Mean blood loss during surgery was 206±216 mL and 281±233 mL for laparoscopic and open surgery, respectively. On the day after surgery (POD1), mean Hb was 9.7±1 g/dL in the IS group and 9.8±1 g/dL in the FC group.

The mean iron deficit calculated using the Ganzoni formula was 1,000 mg for both groups. All patients in the FC group received a single IVI dose of 1,000 mg. The median IVI dose administered in the IS group was 600 mg and most patients (96%) included in group IS were discharged before receiving the total calculated IVI dose.

Mean Hb concentrations at POD4 were 9.9±1.5 and 9.8±1.2 g/dL for the IS and FC groups, respectively. There were no differences in the mean increment in Hb concentrations from POD1 to POD30 between the IS group (2.4 g/dL, 95% CI 2.0-2.8) and the FC group (2.5 g/dL, 95% CI 2.1-2.9); p=0.52. (**Table II**). Mean Hb levels at POD30 were 12.0±1 for IS and 12.2±1.3 g/dL for FC. **Table II** shows the mean change from POD1 to POD30 and from POD4 to POD30 for the PP and the ITT populations. The percentage of patients that reached Hb concentrations

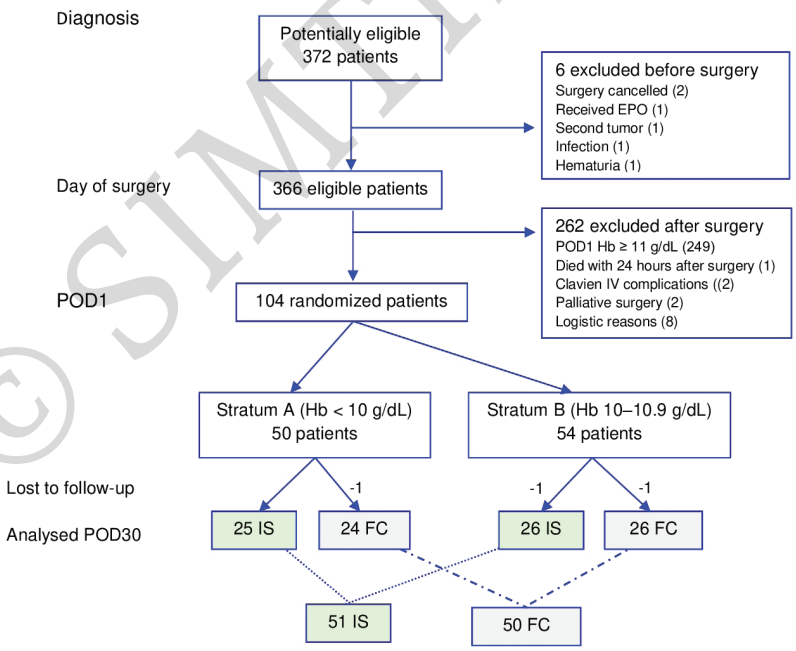


Figure 1 - Patients' characteristics and study groups
One patient in the FC group in stratum A, one in the FC in stratum B, and one in the IS group in stratum B did not receive treatment and were excluded because they were randomised by mistake (they were not eligible for the study).
EPO: erythropoietin; POD1 and 30: postoperative day 1 and 30; IS: iron sucrose; FC: ferric carboxymaltose; Hb: haemoglobin.

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Table I - *Patients' baseline characteristics, and clinical and laboratory data of randomised patients*

Characteristics	IS (n=51)	FC (n=50)
Age, mean (SD), years	71 (12)	73 (10)
Gender, n (%)		
Male	25 (49)	19 (38.0)
Female	26 (51)	31 (62.0)
Bodyweight, mean (SD), kg	68 (13)	70 (15)
ASA classification, n (%)		
I-II	33 (65)	29 (58)
III-IV	18 (35)	21 (42)
Tumour location, n (%)		
Right-transverse colon	20 (39)	16 (32)
Left colon	10 (20)	16 (32)
Rectum	21 (41)	18 (36)
TNM stage, n (%)		
I-II	31 (61)	31 (62)
III-IV	20 (39)	19 (38)
Chemotherapy, n (%)	11 (22)	5 (10)
Haematologic values at diagnosis, mean (SD)		
Hb, g/dL	11.3 (2.2)	11.1 (2)
Transferrin, mg/dL	270.0 (50)	254.5 (58)
TSAT, %	13.4 (9.)	10.6 (5.5)
Ferritin, ng/mL	89.6 (194.7)	102.8(262.8)
Preoperative intravenous iron, n (%)	21 (41)	33 (66)
Hematologic values day of surgery, mean (SD)		
Hb, g/dL	11.4 (1.4)	11.2 (1.6)
Transferrin, mg/dL	209.5 (49.8)	200.8 (52.5)
TSAT, %	21.6 (14.7)	27.5 (19.8)
Ferritin, ng/mL	346.3 (531.4)	472.11(491.7)
Surgical operation n (%)		
Laparoscopy resection	46 (90)	41 (82)
Open resection	5 (10)	9 (18)
Right hemicolectomy	19 (37)	15 (30)
Left hemicolectomy	12 (24)	15 (30)
Subtotal colectomy	0 (0.0)	3 (6)
Rectum resection	20 (39)	17 (34)
Hb value POP1, mean (SD), g/dL	9.7 (1)	9.84 (1)

ASA: American Society of Anesthesiologists; TNM: TNM Tumour Staging System; IS: iron sucrose; FC: ferric carboxymaltose; TSAT: transferrin saturation percentage; POD1: postoperative day 1; Hb: haemoglobin; SD: standard deviation.

≥13 g/dL was 17.6% for IS and 22% for FC; this difference was not statistically significant. **Table II** shows the percentage of patients that reached Hb concentrations ≥11 g/dL and ≥12 g/dL per treatment group.

Differences in changes in Hb concentrations between treatment groups in the different strata (A and B) did not differ from the whole sample (**Table III**). We found no interaction between the treatment group and the variable strata (A or B).

Both ferritin and TSAT levels were higher on the day of surgery than at the time of CRC diagnosis. A slight increase was observed at POD30 (**Figure 2**). Increases in ferritin levels were higher in the FC group.

Exploratory analysis showed that gender, chemotherapy, preoperative treatment with IVI, Hb level on POD1 (<10 g/dL and 10-10.9 g/dL), type of surgery (colon or rectum), and tumour stage were not associated with bigger changes in Hb concentration from POD1 to POD 30. No statistically significant interaction was found between the treatment group (IS or FC) and any of these factors.

Table IV shows the results related to complications of surgery and transfusions received by patients. Overall, 18 patients (17.8%) received an allogeneic blood transfusion; numbers were similar in both treatment groups. Notably, the rate of infections reported was significantly higher in the IS group compared with the FC group (37.2% and 9.8%, respectively). Both IS and FC were well tolerated by all patients. No infusion reactions requiring intervention were registered during the study.

Table II - *Results of primary and secondary endpoints: Per Protocol (PP) and Intention To Treat (ITT) populations*

	IS	FC	p
	Mean (95% CI)	Mean (95% CI)	
PP population (n)	41	42	
Δ Hb POP1 - POP30	2.3 (1.8-2.7)	2.7 (2.2-3.1)	0.164
Δ Hb POP4 - POP30	1.9 (1.5-2.3)	2.5 (2.1-2.9)	
ITT population (n)	51	50	
Δ Hb POP1 - POP30	2.4 (2.0-2.8)	2.5 (2.1-2.9)	0.522
Δ Hb POP4 - POP30	2.1 (1.8-2.5)	2.3 (2.0-2.6)	
	n (%)	n (%)	
Hb ≥13 g/dL at POD30*	9 (18%)	11 (22%)	0.58
Hb ≥11 g/dL at POD30	42 (82%)	45 (90%)	
Hb ≥12 g/dL at POD30	29 (57%)	29 (58%)	

*Key secondary endpoint. Median iron dose administered: 600 mg in iron sucrose (IS) group; 1,000 in ferric carboxymaltose (FC) group. POD1, 4 and 30: postoperative day 1, 4 and 30; Hb: haemoglobin.

Table III - *Changes in haemoglobin (Hb) by strata. Per Protocol (PP) and Intention To Treat (ITT) populations*

	Stratum A (Hb <10g/dL)		Stratum B (Hb 10-10.9g/dL)	
	FS	FC	FS	FC
ITT population, mean (SD)				
Δ Hb POP1 - POP30	2.7(1.4)	2.7 (1.4)	1.7 (1.1)	2 (1.1)
Δ Hb POP4 - POP30	2.5 (1.6)	2.1 (1.9)	1.3 (1.5)	2.5 (1.5)
PP population, mean (SD)				
Δ Hb POP1 - POP30	2.8 (1.2)	2.7 (1.4)	1.8 (0.9)	1.9 (1.1)
Δ Hb POP4 - POP30	2.3 (1.3)	2.5 (1.3)	1.5 (1.6)	2.5 (1.4)

IS: iron sucrose; FC: ferric carboxymaltose; POD1, 4 and 30: postoperative day 1, 4 and 30; SD: standard deviation.

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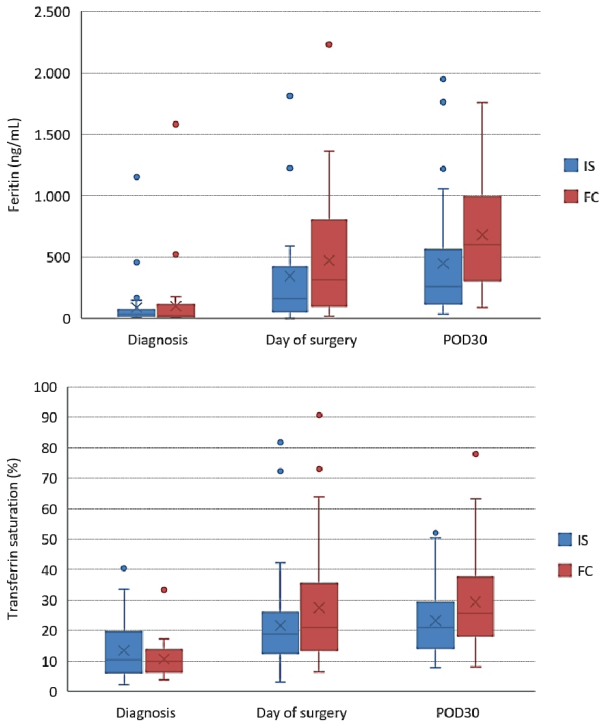


Figure 2 - Ferritin and transferrin saturation at diagnosis of colorectal cancer (CRC), day of surgery, and postoperative day 30 (POD30)
IS: iron sucrose; FC: ferric carboxymaltose.

Table IV - *Surgery complications, transfusions, and hospital length of stay*

	IS (n=50)	FC (n=51)
Blood transfusion		
Subjects transfused, n (%)	10 (19.6)	8 (16)
1 unit **2 units** **3 units** **4 units**	4 (40) 5 (50) 1 (10) 0 (0)	3 (37) 4 (50) 0 (0) 1 (12)
Transfusion index*	1.7	1.8
Infections		
Patients with any infection, n (%) **Infection of the surgical wound** **Intra-abdominal abscess** **Urinary tract infection** **Bacteraemia** **Respiratory infection**	19 (37) 3 (6) 6 (12) 5 (10) 2 (4) 3 (6)	5 (108) 1 (2) 1 (2) 3 (6) 0 (0) 0 (0)
Haemorrhagic complications, n (%)	13 (26)	12 (24)
Cardiovascular complications, n (%)	5 (9)	4 (8)
Length of hospital stay (days), mean (SD) **All patients** **Transfused patients**	 10 (13) 16 (28)	 8 (7) 12 (9)

*Units/patient transfused. IS: iron sucrose; FC: ferric carboxymaltose; POD30: postoperative day 30; Hb: haemoglobin.

DISCUSSION

Our results show that, even if 96% of patients in IS group did not receive the total dose to complete the treatment before hospital discharge, the Hb concentrations reached 30 days after surgery with fractionated IS regimes, were similar to those achieved with the single dose of 1,000 mg of FC. Thus, we could not confirm our hypothesis that treating CRC patients with moderate or severe postoperative anaemia (Hb <11 g/dL) with a single dose of FC, would result in a bigger increase in Hb concentrations at POD30 than treating them with fractionated IS. Differences might have been observed with a longer follow-up.

Notably, we observed that patients with lower Hb concentrations at POD1 (Hb <10 g/dL) had a bigger increase at POD30 (+1 g/dL) compared to those with Hb 10-10.9 g/dL with both regimens of treatment, as previously observed after orthopaedic surgery[21]. This result indicated that those who are more anaemic benefit more from IVI, regardless of the IVI regime used.

Measurement of Hb levels at POD4 is considered more appropriate for defining the presence and severity of postoperative anaemia, as factors such as the haemodilution resulting from surgery procedures are no longer to be considered. In contrast with some studies[22], we observed that in both treatment groups Hb concentrations at POD4 were similar or even higher compared to those at POD1. This finding could be attributed to restricted intraoperative fluid replacement and to the implementation of a fast-track protocol (patients start intake after 6 hours); thus, Hb concentrations were not significantly modified by intravenous fluid administration. In addition, blood losses after laparoscopic CRC surgery are minimal. Consequently, Hb increments from POD4 to POD30 were similar to those from POD1 to POD30.

Preoperative anaemia has been independently associated with adverse outcomes[3,14,16] and guidelines support the treatment of preoperative anaemia to improve patient safety[6,22]. However, few published trials have specifically

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addressed the treatment of postoperative anaemia. The International Consensus on the management of postoperative anaemia after major surgical procedures recommends the early administration of IVI therapy. Where possible, it should be administered using a single high-dose preparation for repletion of iron stores[13,23]. Our institutional protocol for the treatment of perioperative anaemia in CRC surgery recommends the administration of IVI to postoperatively anaemic patients to complete the 1st pillar of the patient blood management (PBM) programme. The main determinants of postoperative anaemia include the presence of preoperative anaemia and the volume of perioperative blood loss[3]. In our study population (n=101), the prevalence of preoperative anaemia at the time of CRC diagnosis was 81.2% (n=82), and 70.7% (n=58) of these patients had iron deficiency. Even though 53.5% (n=54) of them received IV iron to correct iron deficiency anaemia before surgery, 88.1% (n=82) were still anaemic at the time of surgery. The prevalence of anaemia increases after surgery due to blood loss during the procedure and inflammation-induced blunted erythropoiesis. Thus, it is important to identify and treat iron deficiency anaemia also in the postoperative period to improve outcomes in CRC surgical patients.

The percentage of patients who achieved Hb levels >13 g/dL at POD30 was slightly higher among those who received a single dose of FC than among those treated with IS, but no significant between-group differences were noted (23.8% and 19.5%, respectively).

It is important to note that, based on World Health Organization (WHO) anaemia definitions, females achieved a higher percentage of normal Hb values at POD30 as compared to males (54.4% and 20.5%, respectively). Although the WHO has classically established the threshold of Hb level to define anaemia at 13 g/dL for men and 12 g/dL for women, in our work, we have considered the definition proposed by Muñoz *et al.*[24]. According to this, the diagnostic threshold in the peri-surgical context is 13 g/dL for both sexes, taking into account that the classic definition of anaemia would assume that a percentage of women would be underdiagnosed and under-treated, and that they would be exposed to a greater risk of transfusions than men[25].

Our results could question key aspects of the treatment of postoperative anaemia, such as the appropriate time of treatment, the required dose of IVI, the preferred IVI regimen, the desirable therapeutic goal, and how much time is needed to achieve full recovery of Hb levels after treatment, and even the need to administer IVI to those patients who have replenished their iron stores before surgery. In these patients, who had already received IVI before surgery, the amount of IVI necessary to treat postoperative anaemia may be less than that calculated by the Ganzoni formula. Further studies to determine the IVI dose needed to correct postoperative anaemia are needed.

The transfusion rate in this study was higher than expected, taking into account that our institutional restrictive transfusion policy operates within a PBM programme, which includes a preoperative anaemia optimisation protocol. Importantly, the sample included in the study accounted only for anaemic patients with a mean Hb concentration <11 g/dL at POD1 and this circumstance may have accounted for the high transfusion rate observed. We did not find any differences in transfusion rate between groups of treatment, as expected from a study comparing two forms of active iron treatment with no negative control group without IVI treatment. Treatment with IVI during the postoperative period cannot reduce transfusions during the immediate postoperative period since Hb values do not begin to increase for at least 7-14 days. Most of the transfusions took place in the first 2-3 postoperative days and in the context of postsurgical bleeding or in patients who already had moderate-severe anaemia in the preoperative period.

The observed greater incidence of postoperative infection in the IS group compared to the FC group was unexpected. The study was not designed to compare the infection rate, but the significantly lower infection rate in patients treated with FC suggests that the type of molecule could explain this. Garbowski *et al.*[26] showed that different IVI preparations (IS, FC and iron isomaltose) lead to different kinetics of transferrin and non-transferrin bound iron, TSAT and s-ferritin. Such differences may be responsible for differences in iron bioavailability, efficacy, and safety. Both FC and IS consist of a central core of iron and a shell of carbohydrates. The carbohydrate gives stability to the iron and slows its release, thus regulating its pharmacokinetic properties. There are significant differences in iron release depending on the formulation[27]. IS has greater availability

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of free iron and is released faster, as it is a molecule with a higher molecular weight and less stability than that of FC. This is why the observation of a higher infection rate in the group of patients treated with IS could be consistent with an adverse effect of the availability of free iron. On the other hand, Rottemborg *et al.*[28] published a review of available data comparing different IS brands including the original brand (Venofer®, Vifor France S.A., Paris La Défense, France) and other IS, the so-called iron sucrose similars (ISS). Non-clinical studies showed significant differences between all ISS and the original IS in terms of oxidative stress parameters. Different studies included in this review showed elevated oxidative stress and increased levels of inflammatory markers and antioxidant enzymes in the liver, heart, and kidneys of ISS-treated animals. The presence of oxidative stress may be related to a higher risk of infections. This could be an explanation for our results, but further studies are needed to confirm this hypothesis. On the other hand, a pooled analysis of observational data showed that the postoperative administration of IS in orthopaedic surgery did not increase the rate of postoperative infections[29].

This finding underlines the need to design new studies to find out which IVI formulation is safer and more effective, and which is the appropriate dose during the postoperative period.

There was a trend to shorter length of postoperative hospital stay in the FC group compared with the IS group (8 days *vs* 10 days). The higher rate of infections in the IS group may have contributed to the longer length of hospital stay.

Importantly, for the whole study population, transfused patients were hospitalised for longer (16 days in the IS group; 12 days in the FC group). These results are in agreement with previous findings that demonstrated the association of transfusions to longer hospital stay[7,8,10].

As expected[1,14,21,29-32], the two IVI formulations were well tolerated, and no clinically relevant infusion reactions to intravenous administration during hospitalisation were observed.

Limitations of the study

This study has some limitations. First, monitoring Hb levels beyond 30 days could have provided information on when the anaemia is corrected. Kim *et al.*[30] reported that Hb values reached their highest increase at 12 weeks after surgery. This would have given us more information about whether the IVI dose was adequate. Second, we did not study inflammatory parameters (C-reactive protein). These could help to guide postoperative anaemia treatment.

CONCLUSIONS

Patients with moderate-severe postoperative anaemia after CRC surgery showed no difference in the increase in Hb achieved by day 30 regardless of whether they received IS or FC treatment during hospitalisation; unexpectedly lower IVI doses (500 mg IS *vs* 1,000 mg FC) achieved similar results one month after surgery. However, a significantly higher infection rate was observed in patients treated with IS.

Future research will be needed to confirm these results, and to choose the best regime in terms of effectiveness and side effects to treat postoperative anaemia in CRC patients.

ACKNOWLEDGEMENTS

The Authors would like to thank nurses Flori Fernández and Mireia Planas for their enormous help in the difficult task of administering questionnaires and to Marc Fradera for his support in clinical trial monitoring tasks

FUNDING AND RESOURCES

This study is part of a PhD thesis completed by the first Author. Observational results and the study protocol have been published elsewhere. The costs of monitoring the clinical trial were covered with an institutional grant from the Parc Taulí Research Foundation.

AUTHORSHIP CONTRIBUTIONS

Contributors: MJL, CP and RV planned the project and designed data collection tools, monitored data collection for the whole trial, wrote the statistical analysis plan, cleaned and analysed the data, and drafted and revised the paper. MJL, CP and RV wrote the study protocol. EB, JAGE and MM reviewed the protocol. FML and FCB, were members of the clinical study team. MJL and RV were in charge of authorizations. EB, JAGE and MM revised the draft paper and made substantial contributions to the analysis and manuscript. CP and RV directed the project. All Authors reviewed and approved the final version of the manuscript.

DISCLOSURE OF CONFLICTS OF INTEREST

MJ Laso has received honoraria for lectures and travel support from Vifor Pharma outside the submitted work; EB reports

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honoraria for lectures and/or travel support from Vifor Pharma, Sysmex, Takeda, OM Pharma and Zambon outside the submitted work; JAGE reports honoraria for congresses, lectures and/or teaching materials from Uriach-Vifor, Sandoz, Zambon and Jansen outside the submitted work; MM received honoraria for lectures/consultancies from Vifor Pharma Ltd, Pharmacosmos AS, and Zambon, outside the submitted work.

REFERENCES

1. Laso-Morales MJ, Jericó C, Gómez-Ramírez S et al. Preoperative management of colorectal cancer-induced iron deficiency anemia in clinical practice: data from a large observational cohort. Transfusion 2017; **57**: 3040-8.
2. Clevenger B, Richards T. Preoperative anaemia. Anaesthesia 2015; **70** (Suppl 1): 20-8.
3. Muñoz M, Gómez S, Martín E, Auerbach M. Perioperative anemia mangement in colorectal cancer patients: a pragmatic approach. World J Gastroenterol 2014; **20**: 1972-85.
4. Kotzé A, Harris A, Baker CH et al. British Committee for Standards in Haematology Guidelines on the identification and management of preoperative anaemia. Br J Haematol 2015; **171**: 322-31.
5. Musallam KM, Tamim HM, Richards T et al. Preoperative anemia and postoperative outcomes in non-cardiac surgery: a retrospective cohort study. Lancet 2011; **378**: 1396-407.
6. Muñoz M, Acheson AG, Auerbach M et al. International consensus statement on the peri-operative management of anaemia and iron deficiency. Anaesthesia 2017; **72**: 233-47.
7. Acheson AG, Brookes MJ, Spahn DR. Effects of allogeneic red blood cell transfusions on clinical outcomes in patients undergoing colorectal cancer surgery. Ann Surg 2012; **256**: 235-44.
8. Amato A, Pescatori M. Perioperative blood transfusions for the recurrence of colorectal cancer. Cochrane Database Syst Rev 2006; (1): CD005033.
9. Bisbe E, García-Erce JA, Díez-Lobo AI, Muñoz M; Anaemia Working Group España. A multicentre comparative study on the efficacy of intravenous ferric carboxymaltose and iron sucrose for correcting preoperative anaemia in patients undergoing major elective surgery. Br J Anaesth 2011; **107**: 477-8.
10. Calleja JL, Delgado S, del Val A et al. Colon Cancer Study Group. Ferric carboxymaltose reduces transfusions and hospital stay in patients with colon cancer and anemia. Int J Colorectal Dis. 2016; **31**: 543-51.
11. Froessler B, Palm P, Weber I et al. The important role for intravenous iron in perioperative patient blood management in major abdominal surgery: a randomized controlled trial. Ann Surg 2016; **264**: 41-6.
12. Richards T, Baikady R, Clevenger B et al. Preoperative intravenous iron to treat anaemia before major abdominal surgery (PREVENTT): a randomised, double-blind, controlled trial. Lancet 2020; **396**: 1353-61.
13. Muñoz M, Acheson G, Bisbe E et al. An international consensus statement on the management of postoperative anaemia after major surgical procedures. Anaesthesia 2018; **73**: 1418-31.
14. Titos-Arcos JC, Soria-Aledo V, Carrillo-Alcaraz A et al. Is intravenous iron useful for reducing transfusions in surgically treated colorectal cancer patients. World J Surg 2012; **36**: 1893-7.
15. Kalafallah AA, Yan C, Al-Badri R et al. Intravenous ferric carboxymaltose versus standard care in the management of postoperative anaemia: a prospective, open-label, randomised controlled trial. Lancet Haematol 2016; **3**: 415-25.
16. Laso-Morales MJ, Vives R, Gómez-Ramírez S et al. Intravenous iron administration for post-operative anaemia management after colorectal cancer surgery in clinical practice: a single-centre, retrospective study. Blood Transfusion 2018; **16**: 338-42.
17. Ripollés-Melchor J, Ramírez-Rodríguez JM, Casans-Francés R et al. Association between use of enhanced recovery after surgery protocol and postoperative complications in colorectal cáncer surgery. The postoperative outcomes within enhanced recovery after surgery protocol (POWER) study. JAMA surgery 2019; **154**: 725-36.
18. Laso-Morales MJ, Vives R, Vallejo-Tarrat A et al. Single dose of intravenous ferric carboxymaltose infusión versus multiple fractionated doses of intravenous iron sucrose in the treatment of postoperative anaemia in colorectal cáncer patients: study protocol for a randomised controlled trial. Trials 2019; **20**: 23.
19. Clavien PA, Strasberg SM. Severity grading of surgical complications. Ann Surg 2009; **250**: 197-8.
20. Brecher ME, Monk T and Goodnough T. A standardized method for calculating blood loss. Transfusion 1997; **37**: 1070-4
21. Bisbe E, Moltó L, Arroyo R et al. Randomized trial comparing ferric carboxymaltose versus oral ferrous glycine sulphate for postoperative anaemia after total knee arthroplasty. Br J Anaesth 2014; **113**: 402-9
22. Leal-Noval SR, Muñoz M, Asuero M et al. Spanish Consensus Statement on alternatives to allogeneic blood transfusion: the 2013 update of the "Seville Document". Blood Transfus 2013; **11**: 585-610.
23. National Institute for Health and Care Excellence (NICE). Blood transfusion. [NG24]. [Internet]. 2015. Available at: https: //www.nice.org.uk/guidance/ng24/chapter/Recommendations#alternatives-to-blood-transfusion-for-patients-having-surgery. Accessed on 04/06/2019.
24. Muñoz M, Gomez-Ramirez S, Kozek-Langeneker S, Shander A, Richards T, Pavia J et al. "Fit to fly": overcoming barriers to preoperative haemoglobin optimization in surgical patients. Br J Anaesth 2015; **115**: 15-24.
25. Beverina I, Aloni A, Brando B. Impact of gender parity on preoperative anaemia prevalence and patient blood management practice. Blood Transfus 2021; **19**: 396-402.
26. Garbowski MW, Bansal S, Porter JB, et al. Intravenous iron preparations transiently generate non-transferrin-bound iron from two proposed pathways. Haematologica 2021; **106**: 2885-96.
27. Rund D. Intravenous iron: do we adequately understand the short and long term risks in clinical practice? British Journal of Haematology 2021; **193**: 466-80.
28. Rottembourg J. Are iron sucrose and iron sucrose similar equivalent? Analytical, experimental and clinical determinations. Nutri Food Sci J. 2018; **2**: 116.
29. Muñoz M, Gómez-Ramírez S, Cuenca J, García-Erce JA, Iglesias-Aparicio D, Haman-Alcober S, Daniel Ariza, and Enrique Naveira. Very-short-term perioperative intravenous iron administration and postoperative outcome in major orthopaedic surgery: a pooled analysis of observational data from 2547 patients. Transfusion 2014; **54**: 289-99.
30. Kim YW, Bae JM, Park YK et al. Effect of intravenous ferric carboxymaltose on hemoglobin response among patients with acute isovolemic anemia following gastrectomy: the FAIRY randomized clinical trial. JAMA 2017; **317**: 2097-104.
31. Perelman I, Winter R, Sikora L et al. The efficacy of postoperative iron therapy in improving clinical and patient-centered outcomes following surgery: a systematic review and meta-analysis. Transfus Med Rev 2018; **32**: 89-101.
32. Avni T, Bieber A, Grossman A, et al. The safety of intravenous iron preparations: systematic review and meta-analysis. Mayo Clin Proc. 2015; **90**: 12-23.

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