Short-term effect of preoperative intravenous iron therapy in colorectal cancer patients with anemia: results of a cohort study

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BACKGROUND: In the treatment of preoperative anemia, which is associated with increased postoperative morbidity, iron supplementation can replace blood transfusion and erythropoiesis-stimulating agents. The aim of this study was to assess the efficacy of preoperative intravenous (IV) iron infusion in optimizing hemoglobin (Hb) levels in anemic colorectal cancer patients.

STUDY DESIGN AND METHODS: A retrospective cohort study was performed on patients who underwent surgery for colorectal cancer between 2010 and 2016 in a single teaching hospital. The primary outcome measure, the change in Hb level, was assessed by comparing anemic patients receiving usual care (UC; i.e. no iron therapy and no blood transfusion) with anemic patients receiving IV iron therapy (no blood transfusion).

RESULTS: A total of 758 patients with colorectal cancer were eligible, of whom 318 (41.9%) had anemia. The IV and the UC groups included 52 and 153 patients with mean Hb levels at diagnosis of 6.3 and 6.9 mmol/L, respectively. In the IV group, preoperative Hb level was significantly increased compared to the UC group (0.65 mmol/L vs. 0.10 mmol/L, $p < 0.001$). High increase in Hb level after iron infusion was associated with initial higher transferrin and lower ferritin levels (high vs. poor responders: median transferrin 2.9 g/L vs. 2.7 g/L, median ferritin 12 μg/L vs. 27 μg/L).

CONCLUSION: Implementation of IV iron therapy in anemic colorectal cancer patients leads to a distinct increase of preoperative Hb level. IV iron therapy is most effective in patients presenting with more severe anemia, and with higher transferrin and lower ferritin levels, markers for an absolute iron deficiency (ID), compared to functional ID.

Colorectal cancer is the third most commonly diagnosed cancer in men and second in women worldwide,[1] and patients present with anemia in up to one-third of the cases.[2] Anemia in this respect is emerging as an important health problem. It is not only associated with fatigue[3] and

ABBREVIATIONS: AID = absolute iron deficiency; ASA = American Society of Anesthesiologists; FID = functional iron deficiency; ID = iron deficiency; PBM = patient blood management; UC = usual care.

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impaired physical performance and cognitive function, but most importantly also with increased morbidity and mortality.[4-6]

Iron deficiency (ID) is the most common cause of preoperative anemia in colorectal cancer patients.[7] Contributing mechanisms to the development of ID anemia include chronic tumor-induced blood loss and also impaired iron homeostasis associated with chronic disease. While chronic blood loss will cause absolute ID (AID), characterized by depleted iron stores, impaired iron homeostasis will cause functional ID (FID), characterized by reduced iron uptake and iron mobilization from the reticuloendothelial system, both leading to a reduction of biologically available iron for erythropoiesis.[8]

Enhancement of a patient's condition before surgery has been gaining attention ever since the beneficial outcomes of such protocols were shown.[9,10] More specifically, normalization of preoperative hemoglobin (Hb) level by blood management strategy is an important element in this spectrum of preoperative care.[11-13]

The high prevalence of ID anemia in colorectal cancer patients provides an opportunity to optimize preoperative Hb level by preoperative iron supplementation with the purpose of reducing the use of blood transfusions and erythropoiesis-stimulating agents.[14] Avoiding blood transfusions and erythropoiesis-stimulating agents in oncologic patients seems important because of its association with an increased risk of cancer recurrence and increased mortality.[15-17] Oral iron has been shown to correct anemia, but is also known to be slow in terms of absorption rate, to cause constipation, and to be ineffective in patients with FID as oral iron is poorly absorbed in the duodenum in these patients, due to increased production of hepcidin.

Therefore, compared to oral iron, intravenous (IV) iron therapy is likely to be more effective in treating anemia, as shown in patients undergoing orthopedic[18] or general abdominal surgery.[19] Based on these advantages, over the course of the past 5 years administration of IV iron has also been introduced in our institution. In this study, we retrospectively compare preoperative IV iron with usual care (UC; i.e., no iron therapy) in colorectal cancer patients with anemia, with regard to increasing preoperative Hb level, and reducing postoperative complications and blood transfusions. In addition, predictive factors of good response to IV iron therapy will be studied.

MATERIALS AND METHODS

Patient selection

All patients undergoing resection for colorectal cancer between January 1, 2010, and July 1, 2016, at the Department of Surgery, Reinier de Graaf Hospital, the Netherlands, were identified. Patients who had surgery in the emergency setting and those with missing data with respect to baseline Hb levels and blood transfusions were excluded.

Outcome measures

Primary outcome was the change in Hb level (i.e., Hb at diagnosis – Hb preoperative), and secondary outcomes included the percentage of patients with a blood transfusion and complication less than 30 days postoperatively.

Defining patient groups

Consecutive patients diagnosed with anemia (men Hb < 8.0 mmol/L, 12.9 g/dL; women Hb < 7.5 mmol/L, 12.0 g/dL) were eligible for inclusion. Initially, to provide a clear overview, the total cohort with anemia was divided in two main groups (IV vs. UC).

The UC group consisted of patients receiving UC, defined by no IV iron therapy less than 6 weeks before surgery. In general and after the disadvantages of oral iron supplementation, none of the patients awaiting surgery in our center did receive preoperative oral iron therapy. According to the criteria of the Dutch Blood Transfusion Guideline, during the entire study period, a blood transfusion was given according to the 4-5-6 rule, depending on the severity of the anemia and the condition of the patient.[20]

The IV group consisted of patients receiving IV iron therapy less than 6 weeks before surgery, defined by a dose of 1000 to 2000 mg of iron(III)carboxymaltose (Ferinject) or iron(III)isomaltoside (Monofer). In our institution, a patient blood management (PBM) protocol was implemented in July 2013. Before implementation of this protocol, treatment of preoperative anemia was heavily depending on the interest in, and knowledge of, PBM of each physician. As a result, there was heterogeneity in the cohort of patients with anemia treated with IV iron therapy before July 2013. As part of the implemented PBM protocol, iron status was measured in all consecutive patients diagnosed with colorectal cancer and treatment with IV iron therapy was considered for patients with anemia. However, each physician did have the possibility to deviate from the PBM protocol, depending on their clinical assessment. As a result, there was also heterogeneity in the cohort of patients with anemia treated with IV iron therapy after July 2013. Due to this heterogeneity, comparing a before and after July 2013 cohort would not yield relevant results.

In addition, two subgroups (IV vs. UC) were formed, in which all factors possibly directly affecting Hb level (i.e., preoperative blood transfusion and neoadjuvant chemotherapy) were excluded. Patients receiving their first IV iron infusion less than 7 days before surgery (IV group),

and patients receiving IV iron infusion between 6 and 12 weeks before surgery (UC group) were additionally excluded.

Statistical analyses

To assess the primary outcome, the difference between Hb level at diagnosis and preoperative Hb level were calculated and analyzed in the two subgroups. In addition, predictive factors of good response to IV iron were identified. For comparison, chi-square and Mann-Whitney U tests were performed. To assess the association between IV iron therapy and postoperative blood transfusion and complication, all patients with anemia (i.e., UC + IV group) were included in uni- and multivariable logistic regression analyses. Among the variables included in the logistic regression analyses is time frame surgery (2014-2016 vs. 2010-2013), because in the course of time new surgical techniques or procedures could potentially contribute to a decrease in the postoperative blood transfusion and complication rate. A significance level of 0.05 was considered to be significant.

Data collection

The use of preoperative IV iron therapy and pre-, peri-, and postoperative blood transfusion was retrospectively collected. In this respect, preoperative period was defined as less than 6 weeks before surgery and postoperative period as less than 30 days after surgery. In addition, Hb values at diagnosis of colorectal cancer, before operation (i.e., 1 day before surgery), and after operation (i.e., 1 day after surgery) were manually obtained from medical records. Clinical and pathologic data, including age, sex, American Society of Anesthesiologists physical status classification (ASA classification), overall comorbidities (i.e., cardiologic, vascular, diabetes, pulmonic, neurologic, thrombotic, urologic, musculoskeletal, infectious, malignancy, endocrine) tumor type, pathologic tumor stage, neoadjuvant treatment, and postoperative overall complications (i.e., pulmonic, cardiologic, thrombotic, infectious, neurologic) were collected by the Dutch Surgical Colorectal Audit, a disease-specific national audit.[21] This audit collects information on patient, tumor, treatment, and 30-day and in-hospital outcome characteristics of all patients undergoing a resection for primary colorectal carcinoma in the Netherlands. The data set is based on evidence-based guidelines and is cross-checked on a yearly basis with data from the Netherlands Cancer Registry.

Ethical approval for this study was provided by the Ethical Committee METC Zuidwest Holland (METC-nr 16-012, approved by secretary mw. drs. E. Roep, date of approval 03/02/2016). Our institution, a teaching hospital, is making use of opt-out consent. Each included patient had given consent by not declining to give consent.

RESULTS

In total, 916 patients underwent surgery for colorectal cancer. A total of 158 patients were excluded because of missing data on blood transfusion or Hb level at diagnosis or surgery in the emergency setting. A total of 318 patients (41.9%) had anemia at diagnosis, of whom 94 patients received IV iron treatment and 224 patients received UC. After all factors possibly directly affecting Hb level were excluded, 52 and 153 patients remained in the IV and UC subgroup (Fig. 1).

IV versus UC, total cohort with anemia

An overview of the baseline characteristics is presented in Table 1. Both groups had a mean age of more than 70 years (IV, 71.8 ± 11.1; UC, 73.7 ± 9.9; $p = 0.15$). In the UC group, the majority was male compared to the IV group (58.5% vs. 44.7%; $p = 0.02$) and there were more patients with comorbidity (87.1% vs. 79.8%; $p = 0.01$) and with a rectum tumor (20.5% vs. 5.3%; $p = 0.001$). Regarding physical condition, surgical procedure, and tumor stage, no significant differences were found. In the IV group, Hb level at diagnosis was significantly lower (6.12 mmol/L vs. 6.61 mmol/L; $p < 0.001$) and more patients received a preoperative blood transfusion (31.9% vs. 12.9%; $p < 0.001$). Of 30 IV patients additionally receiving a preoperative blood transfusion, 13 patients (mean Hb level at diagnosis of 5.7 mmol/L) received blood transfusion before iron infusion, while in 17 patients (mean Hb level at diagnosis of 5.7 mmol/L) blood infusion was administered after iron transfusion. Mean Hb level at diagnosis was considerably higher in IV patients who did not receive preoperative blood transfusion (6.3 mmol/L).

IV versus UC, subgroup

An overview of the baseline characteristics is presented in Table 2. In total, 105 patients were included (IV, 52; UC, 153). In the IV group, 32 and 20 patients received a 1000 to 2000mg dose of iron(III)isomaltoside and iron(III)carboxymaltose, respectively. Both groups had a mean age of more than 70 years (IV, 71.3 ± 11.6; UC, 74.3 ± 9.5; $p = 0.09$). In the UC group, more males were included compared to the IV group (60.8% vs. 44.2%; $p = 0.04$) and there were more patients with a high ASA score (34% vs. 19.2%; $p = 0.04$). In the IV group, significantly more patients were operated laparoscopically (82.7% vs. 64.7%; $p = 0.02$). Regarding comorbidity, tumor localization and tumor stage, no significant differences were found. In the IV group, Hb level at diagnosis was significantly lower (6.3 mmol/L vs. 6.9 mmol/L; $p < 0.001$).

Patients with IV iron treatment showed a significantly higher increase of Hb level compared to patients with UC (IV 0.65 mmol/L vs. UC 0.10 mmol/L; $p < 0.001$). In

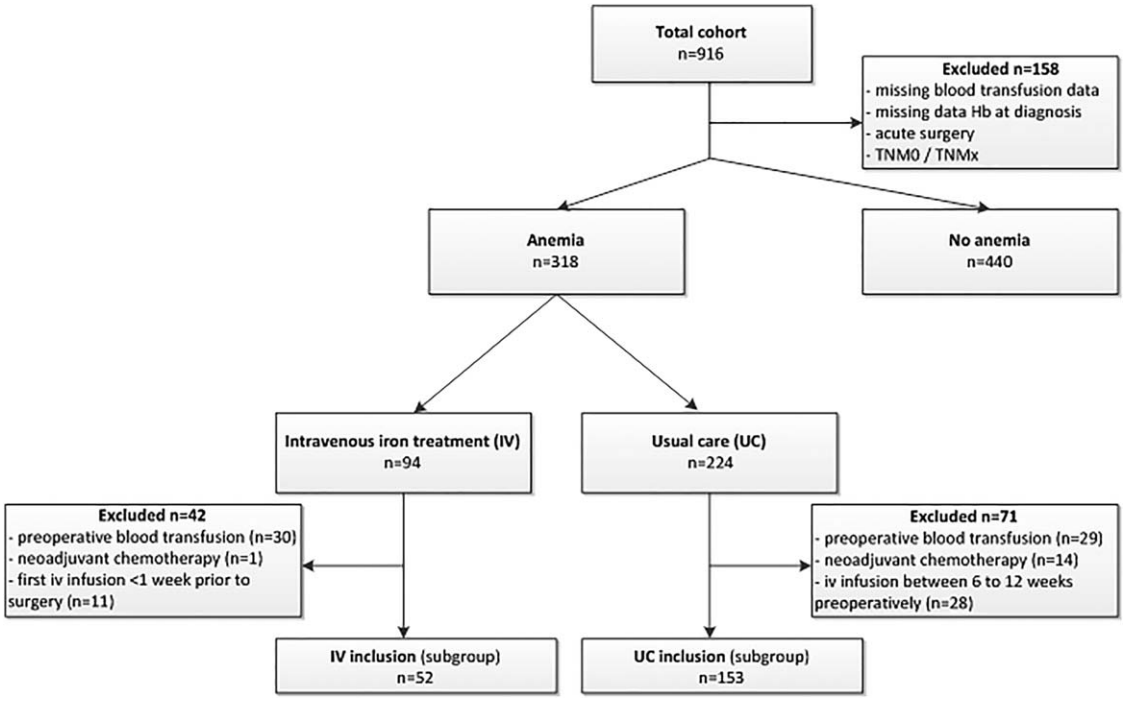

Fig. 1. Flow diagram.

TABLE 1. Patient baseline characteristics of all patients with anemia at diagnosis, IV group versus UC group*

Characteristic	IV group (n = 94)	UC group (n = 224)	p value
Age (years)	71.8 ± 11.1	73.7 ± 9.9	0.15
Sex (male)	42 (44.7)	131 (58.5)	0.02
ASA classification			0.06
I-II	71 (75.5)	145 (64.7)	
III-IV	23 (24.5)	79 (35.3)	
Comorbidity (overall)	75 (79.8)	195 (87.1)	0.01
Tumor localization			0.001
Colon	89 (94.7)	178 (79.5)	
Rectum	5 (5.3)	46 (20.5)	
TNM stage			0.68
I-II	59 (62.8)	135 (60.3)	
III-IV	35 (37.2)	89 (39.7)	
Surgery			
Time frame			0.06
2010-2013	53 (56.4)	151 (67.4)	
2014-2016	41 (43.6)	73 (32.6)	
Laparoscopic (%)	72 (76.6)	153 (68.3)	0.14
Hb (mmol/L)			
At diagnosis	6.12 ± 0.89	6.61 ± 0.87	<0.001
Number patients with preop. BT (%) | Hb at diagnosis (mmol/L)			<0.001
Yes	30 (31.9) | 5.67	29 (12.9) | 5.56	
Before iron infusion	13 | 5.68	NA	
After iron infusion	17 | 5.67	NA	
No	64 (68.1) | 6.32	195 (87.1) | 6.77	
Number patients with postop. BT (%) | number of units transfused			
Yes	10 (10.6) | 28	45 (20.1) | 91	
No	84 (89.4)	179 (79.9)	
Number patients with postop. complication (%)			
Yes	24 (25.5)	77 (34.4)	
No	70 (74.5)	147 (65.6)	

*Data are reported as mean ± SD or number (%)
BT = blood transfusion; postop. = postoperative; preop. = preoperative; TNM = tumor, node, and metastasis.

TABLE 2. Patient baseline characteristics and outcome, IV subgroup versus UC subgroup*

Characteristics	IV (n = 52)	UC (n = 153)	p value
Age (years)	71.3 ± 11.6	74.3 ± 9.5	0.09
Sex (male)	23 (44.2)	93 (60.8)	0.04
ASA classification			0.045
I-II	42 (80.8)	101 (66.0)	
III-IV	10 (19.2)	52 (34.0)	
Comorbidity (overall)	11 (21.2)	21 (13.7)	0.20
Tumor localization			0.08
Colon	48 (92.3)	126 (82.4)	
Rectum	4 (7.7)	27 (17.6)	
TNM stage			0.36
I-II	34 (65.4)	89 (58.2)	
III-IV	18 (34.6)	64 (41.8)	
Surgery			
Time frame			0.31
2010-2013	31 (59.6)	103 (67.3)	
2014-2016	21 (40.4)	50 (32.7)	
Laparoscopic (%)	43 (82.7)	99 (64.7)	0.02
Hb (mmol/L)			
At diagnosis	6.3 ± 0.8	6.9 ± 0.7	<0.001
Outcome Hb (mmol/L) increase diagnosis-preop.	0.65 ± 0.74	0.10 ± 0.74	<0.001

*Data are reported as mean ± SD or number (%)
preop. = preoperative; TNM = tumor, node, and metastasis.

TABLE 3. Patient baseline characteristics, high responder (≥0.6 mmol/L Hb increase) versus poor responder (<0.6 mmol/L Hb increase), receiving one-dose iron infusion (1000 mg)*

Characteristics	IV high responder (n = 17)	IV poor responder (n = 16)	p value
Age (years)	69.3 ± 13.1	73.6 ± 9.0	0.28
Sex (male)	5 (29.4)	5 (31.2)	0.91
ASA classification			1.0
I-II	13 (76.5)	13 (81.2)	
III-IV	4 (23.5)	3 (18.8)	
Comorbidity (overall)	14 (82.4)	12 (75.0)	0.69
Tumor localization			0.60
Colon	16 (94.1)	14 (87.5)	
Rectum	1 (5.9)	2 (12.5)	
TNM stage			0.62
I-II	12 (70.6)	10 (62.5)	
III-IV	5 (29.4)	6 (37.5)	
Iron status at diagnosis			
Hb (mmol/L)	6.0; 1.5 – 6.2 ± 0.8	6.8; 1.1 – 6.6 ± 0.7	0.10
TSAT (%)	5.3; 4.6 – 7.3 ± 4.6	11; 15 – 16.3 ± 14.3	0.02
Transferrin (g/L)	2.9; 0.4 – 3.1 ± 0.5	2.7; 0.2 – 2.7 ± 0.4	0.02
Ferritin (μg/L)	12; 27 – 36 ± 52	27; 67 – 142 ± 360	0.13

*Data are reported as mean ± SD, number (%), or median; IQR – mean ± SD.
TNM = tumor, node, and metastasis; TSAT = transferrin saturation.

identifying characteristics associated with Hb level response after iron infusion, patients receiving one dose of iron infusion (1000 mg) were classified into high and poor responders. A cutoff value of 0.6 mmol/L (i.e., median Hb level increase) was used (Table 3). In total, 33 patients were included (high responder, 17; poor responder, 16). No significant differences were found for age, sex, ASA score, comorbidity, tumor localization, and tumor stage. Regarding iron status at diagnosis, high responders showed more distinct signs of anemia and ID compared to poor responders (high vs. poor responder; median values, Hb 6.0 mmol/L vs 6.8 mmol/L, transferrin saturation 5.3% vs. 11%). In addition, increased transferrin (median, 2.9 g/L vs. 2.7 g/L) and decreased ferritin (median, 12 μg/L vs. 27 μg/L) levels were found in the high-responder group.

Association between IV iron therapy and postoperative complications and blood transfusions

All patients with anemia, as presented in Table 1, were included in logistic regression analyses. In univariable analysis, preoperative IV iron administration (odds ratio [OR], 0.47; 95% confidence interval [CI], 0.23-0.99;

TABLE 4. Regression analysis on relationship between preoperative IV iron and postoperative blood transfusion in patients with anemia (n = 318)

	Univariable			Multivariable		
Characteristics	OR	95% CI	p value	OR	95% CI	p value
Age (years)	1.02	0.99-1.05	0.23	1.02	0.99-1.06	0.26
Sex						
Female vs. male	0.69	0.38-1.26	0.23	0.52	0.27 1.04	0.06
Comorbidity (overall)	1.27	0.54-2.99	0.59	1.04	0.39 2.74	0.94
ASA classification						
III-IV vs. I-II	1.84	1.01-3.33	0.045	1.77	0.89-3.53	0.11
TNM stage						
III-IV vs. I-II	0.72	0.39-1.33	0.30	0.66	0.34-1.28	0.22
Surgery						
Laparoscopic vs. open	0.51	0.28-0.92	0.026	0.55	0.28-1.06	0.08
Tumor localization						
Rectum vs. colon	1.03	0.47-2.26	0.94	1.10	0.98-1.24	0.12
Time frame surgery						
2014-2016 vs. 2010-2013	0.69	0.37-1.30	0.25	0.65	0.32-1.32	0.24
Preoperative Hb (0.1 mmol/L increase)	0.48	0.33-0.69	<0.001	0.40	0.26-0.60	<0.001
Preoperative IV iron	0.47	0.23-0.99	0.046	0.54	0.24-1.21	0.14

TNM = tumor, node, and metastasis.

TABLE 5. Regression analysis on relationship between preoperative IV iron and postoperative complications in patients with anemia (n = 318)

	Univariable			Multivariable		
Characteristics	OR	95% CI	p value	OR	95% CI	p value
Age (years)	1.01	0.99-1.03	0.51	1.02	0.99-1.04	0.30
Sex						
Female vs. male	0.43	0.26-0.70	0.001	0.36	0.20-0.63	<0.001
Comorbidity (overall)	0.67	0.35-1.26	0.21	0.48	0.23-0.99	0.049
ASA classification						
III-IV vs. I-II	1.54	0.94-2.53	0.09	1.62	0.90-2.90	0.11
TNM stage						
III-IV vs. I-II	0.76	0.47-1.25	0.28	0.58	0.34-1.00	0.050
Surgery						
Laparoscopic vs. open	0.33	0.20-0.55	<0.001	0.32	0.18-0.55	<0.001
Tumor localization						
Rectum vs. colon	1.09	0.58-2.06	0.79	1.03	0.94-1.13	0.54
Time frame surgery						
2014-2016 vs. 2010-2013	0.99	0.60-1.62	0.96	0.94	0.54-1.63	0.81
Preoperative Hb (0.1 mmol/L increase)	1.12	0.85-1.47	0.44	1.08	0.79-1.48	0.65
Preoperative IV iron	0.66	0.38-1.12	0.12	0.91	0.50-1.68	0.77

TNM = tumor, node, and metastasis.

p = 0.04) was observed to prevent the administration of postoperative blood transfusion. No significant result was found in multivariable analysis (OR, 0.54; 95% CI, 0.24-1.21; p = 0.14; Table 4). In both uni- and multivariable analysis, no advantageous effect was found on postoperative complications (OR, 0.66; 95% CI, 0.28-1.12; p = 0.12; and OR, 0.91; 95% CI, 0.50-1.68; p = 0.77, respectively; Table 5).

DISCUSSION

This study illustrates the efficacy of IV iron therapy in the optimization of preoperative Hb level in colorectal cancer patients with anemia, compared to UC. We found that IV iron therapy is most effective in patients presenting with more severe anemia and with higher transferrin and lower ferritin levels, markers for an AID, compared to FID. In this study, the distinct Hb increase after iron infusion did not translate into an expected decrease in the percentage of patients with a postoperative blood transfusion. This is most likely due to the confounding effect of preoperative blood transfusions, which could not be adequately corrected for in this retrospective cohort. Our observed perioperative blood transfusion rates are fairly comparable with the perioperative blood transfusion rates presented in other large cohort studies,[22,23] and our results, therefore, could legitimately be generalized.

Our results add to a growing body of evidence in the literature demonstrating the efficacy of preoperative IV iron therapy in colorectal cancer patients and contribute

to the ongoing debate whether preoperative IV iron therapy is improving postoperative outcome. Our results are consistent with the results of a prospective randomized trial by Keeler and colleagues,[24] comparing the effect of preoperative oral versus IV iron in colorectal cancer patients with anemia. No overall benefit was seen with IV iron in reducing blood transfusions and postoperative complications, despite the fact that in the study by Keeler and colleagues oral iron administration represented UC. However, in addition to the study by Keeler and colleagues, we also identified patients characteristics associated with Hb level response after iron infusion. Evidently, higher transferrin and lower ferritin levels, markers for AID, were associated with a higher Hb level response after iron infusion. Increased ferritin level, a marker for FID, could be the cause of poor Hb level response after iron infusion. In this respect, increased uptake and retention of the administered IV iron within cells of the reticuloendothelial system may lead to a poor availability of administered iron for erythropoiesis.[8] Therefore, these results stress the importance of distinguishing between the two types of ID and emphasize the efficacy of IV iron namely in patients with AID. It is noteworthy that in present international guidelines on the treatment of anemia in oncologic patients a distinction between type of ID is already made: IV iron should be withheld in patients with an active infection and/or if serum ferritin exceeds 1000 μg/L.[25,26] Despite this, in current clinical practice, no distinction is made between type of ID. Ongoing and future randomized clinical trials must establish whether the optimization of preoperative Hb level by preoperative IV iron therapy is resulting in improved postoperative outcome.[11,13]

A key strength of our study is the identification of patient characteristics associated with Hb level response after iron infusion in colorectal cancer patients. To our knowledge, this is the first study identifying the potential clinical relevance of identifying the type of ID in the treatment of preoperative anemia not only with oral iron but even with IV iron.

The main limitations of our study are threefold, leading to key recommendations for future research. First, this study represents a retrospective cohort of consecutive patients, involving several limitations. The significant differences between the IV iron and UC group (e.g., baseline Hb levels and time frame surgery) could, despite correction in the multivariable regressions analyses, potentially indicate selection bias and have significant impact on the outcome. Moreover, iron status was not consistently monitored in each patient. In the past years, great efforts have been made to optimize the results of colorectal cancer surgery. In addition to surgical techniques and procedures,[9,10,27] blood transfusion strategy, as part of PBM, has also changed in the course of time. In this regard, the optimal transfusion threshold, dosing, and age of red blood cell (RBC) units have been studied. At present, a restrictive transfusion threshold is recommended for hospitalized adult patients and seems to be safe in the oncologic setting.[28,29] Moreover, standard-issue RBC units rather than fresh RBC units (storage length, <10 days) and, to initiate, 1 rather than 2 RBC units are advised.[29] Although we corrected our results for the year of treatment, the combined efforts to optimize colorectal cancer care (e.g., centralization, protocols, laparoscopy) might have contributed differently to the results. This emphasizes the importance of performing a randomized controlled trial comparing UC (i.e., no therapy or oral iron) with IV iron supplementation in colorectal cancer patients in which, importantly, IV iron must be administered as early as possibly, preferably at least 3 weeks before surgery for its optimal effect.[11]

Second, this study focused specifically on preoperative treatment of anemia. However, investigation and treatment of merely Hb levels appears to be a suboptimal way to indicate overall performance and therefore, at present, various multimodal programs are being introduced.[30,31] The use of such various modalities could be valuable in preoperative prehabilitation, specifically in elderly patients (>75 years), in which an increased 1-year mortality of up to 25% is observed.[32,33] In line with the previous limitation, in this study, various multimodal programs may similarly introduce confounding of our results that are not easily corrected for. A randomized trial could correct for both continuing pre- as well as postoperative care optimization.

The third limitation was that only short-term effects of IV iron therapy were studied. In this respect, iron is an important growth factor for rapidly proliferating cells, including bacteria and tumor cells.[8,34] Several animal experiment studies have shown exposure to iron to be a risk factor for developing colorectal cancer and tumor growth.[35,36] In this regard, intraluminal colorectal tumors might be more affected by oral iron administration, while IV iron with a higher risk of non–transferrin-bound serum iron and reactive oxygen species presence might also influence systemic tumor growth. Randomized trials on the short-term benefits versus the potential long-term hazards of iron therapy in colorectal cancer patients should therefore acknowledge the type of anemia and the associated choice of iron therapy.

In conclusion, we were able to show that implementation of IV iron therapy leads to optimization of preoperative Hb level. Furthermore, we showed the importance of assessing the type of ID. Iron infusion is most effective in patients with more severe anemia and with higher transferrin and lower ferritin levels, markers for AID, compared to FID. After the optimization of preoperative Hb level, strikingly, no significant decrease in the percentage of patients with a postoperative blood transfusion and postoperative complication were observed. However, from this cohort study, due to its retrospective nature, we cannot

entirely conclude that IV iron and the associated Hb increase does decrease the postoperative blood transfusion and complication rate. Future randomized trials are thus required to not only establish the short-term benefits, but also the potential long-term hazards of preoperative IV iron therapy in colorectal cancer patients.

CONFLICT OF INTEREST

The authors have disclosed no conflicts of interest.

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