Preoperative blood management in colorectal cancer surgery: the controversial role of iron

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Chapter 4 // **Short-term effect of preoperative intravenous iron therapy in anemic colorectal cancer patients: results of a cohort study**

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ABSTRACT

Background: Preoperative anemia is associated with increased postoperative morbidity and delayed recovery in oncological patients. In the treatment of such anemia , iron suppletion can replace blood transfusion and erythropoiesis-stimulating agents, which both have been associated with substantial side effects and increased risk of cancer recurrence. The aim of this study was to assess the efficacy of preoperative intravenous iron infusion in optimising hemoglobin (Hb) level in anemic colorectal cancer patients and to identify patient characteristics that are associated with an increase in Hb level after iron infusion.

Methods: A retrospective cohort study was performed on patients who underwent surgery for colorectal cancer between 2010-2016 in a single teaching hospital. The primary outcome measure, the change in hemoglobin level, was assessed by comparing anemic patients receiving usual care (UC)(i.e. no iron therapy and no blood transfusion) with anemic patients receiving intravenous iron (IV) therapy (no blood transfusion). In addition, in assessing the association between intravenous iron therapy and postoperative blood transfusions and complications, all anemic patients were included in logistic regression analyses.

Results: 758 patients with colorectal cancer were eligible, of which 318 (41.9%) were anemic. The IV and the UC group 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 as compared to 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 versus poor responders: median transferrin 2.9 vs 2.7 g/L, median ferritin 12 vs 27 µg/L). Multivariable logistic regression analyses on all anemic patients (n=318) showed that administration of intravenous iron therapy did not affect postoperative blood transfusion and complication rate (OR 0.54, p=0.14 and OR=0.91, p=0.77, respectively).

Discussion: Based on this cohort study, implementation of intravenous iron therapy in anemic colorectal cancer patients leads to a distinct increase of preoperative hemoglobin level. Intravenous 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, as compared to functional iron deficiency. Our finding, that the distinct Hb increase did not coincide with an expected decrease in the percentage of patients with a postoperative blood transfusion or complication, should be viewed with caution due to the retrospective nature of this study. Future randomised trials are thus required to establish the short-term benefits.

INTRODUCTION

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 a third of the cases.[2] Anemia in this respect is emerging as an important health problem. It is not only associated with fatigue[3], 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 iron deficiency anemia (IDA) include chronic tumour-induced blood loss and also impaired iron homeostasis associated with chronic disease. While chronic blood loss will cause absolute iron deficiency (AID), characterized by depleted iron stores, impaired iron homeostasis will cause functional iron deficiency (FID), characterized by reduced iron uptake and iron mobilisation from the reticulo-endothelial system, both leading to a reduction of biologically available iron for erythropoiesis.[8]

Enhancement of a patient's condition prior to 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 IDA in colorectal cancer patients provides an opportunity to optimise preoperative hemoglobin level by preoperative iron supplementation with the purpose of reducing the use of blood transfusions and erythropoiesis-stimulating agents (ESAs).[14] Avoiding blood transfusions and ESAs in oncological 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 as compared to oral iron, intravenous 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 last five years administration of intravenous iron has also been introduced in our institution. In this study, we retrospectively compare preoperative intravenous iron with usual care (i.e. no iron therapy) in anemic colorectal cancer patients, with regard to increasing preoperative hemoglobin level, and reducing postoperative complications and blood transfusions. In addition, predictive factors of good response to intravenous iron therapy will be studied.

METHODS

Patient selection

All patients undergoing resection for colorectal cancer between 1 January 2010 and 1 July 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 hemoglobin level (i.e. Hb at diagnosis – Hb preoperative), secondary outcomes included the percentage of patients with a blood transfusion and complication <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 anemic cohort was divided in two main groups (IV versus UC).

The UC group consisted of patients receiving usual care, defined by no intravenous iron therapy <6 weeks prior to surgery. In general and following the disadvantages of oral iron suppletion, 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 intravenous iron therapy <6 weeks prior to surgery, defined by a dose of 1000-2000mg iron(III)carboxymaltose (Ferinject) or iron(III)isomaltoside (Monofer). In our institution, a patient blood management protocol (PBM) was implemented in July 2013. Prior to 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 anemic patients treated with intravenous 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 intravenous 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 anemic patients treated with intravenous 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 intravenous iron infusion <7 days prior to surgery (IV group), and patients receiving intravenous iron infusion between 6 and 12 weeks prior to 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 analysed in the two subgroups. In addition, predictive factors of good response to intravenous iron were identified. For comparison, $\chi 2$ and Mann Whitney U tests were performed. To assess the association between intravenous iron therapy and postoperative blood transfusion and complication, all anemic (i.e. UC + IV group) patients were included in uni- and multivariable logistic regression analyses. Amongst the variables included in the logistic regression analyses is timeframe 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 statistical significant.

Data Collection

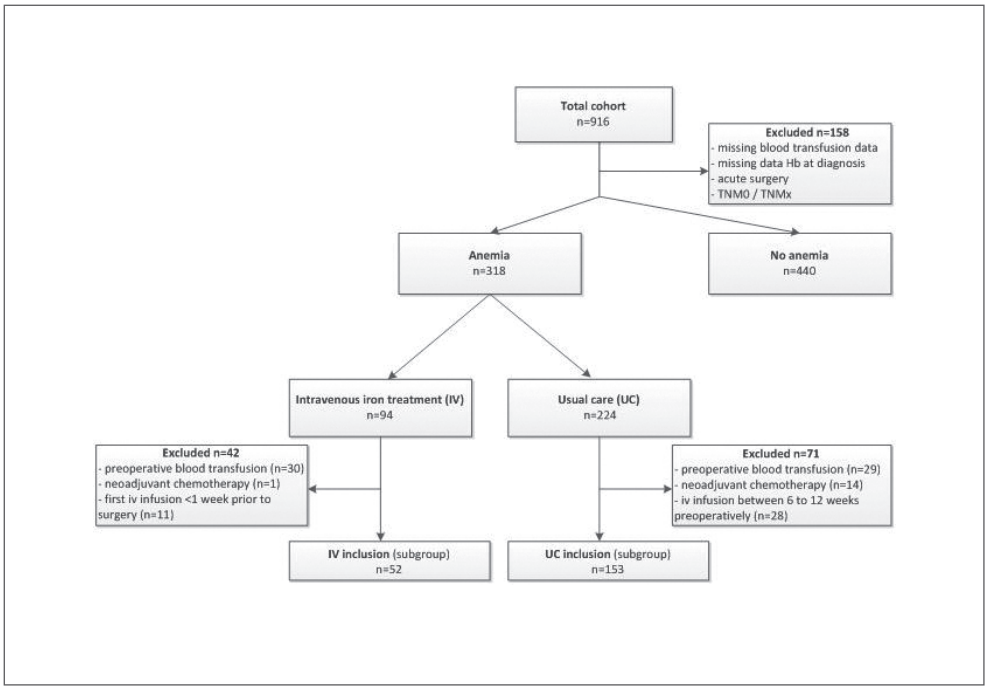
The use of preoperative intravenous iron therapy and pre-, peri-, and postoperative blood transfusion was retrospectively collected. In this respect, preoperative period was defined as <6 weeks before surgery, and postoperative period as <30 days after surgery. In addition, Hb values at diagnosis of colorectal cancer, preoperative (i.e. one day before surgery) and postoperative (i.e. one day after surgery) were manually obtained from medical records. Clinical and pathological data, including age, gender, ASA-classification (i.e. American Society of Anesthesiologists physical status classification), overall comorbidities (i.e. cardiologic, vascular, diabetes, pulmonic, neurologic, thrombotic, urologic, musculoskeletal, infectious, malignancy, endocrine) tumor type, pathological tumor stage, neoadjuvant treatment, and postoperative overall complications (i.e. pulmonic, cardiologic, thrombotic, infectious, neurologic) were collected by the Dutch Surgical Colorectal Audit (DSCA), a disease-specific national audit.[21] This audit collects information on patient, tumour, 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 patients 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%) were anemic at diagnosis, of which 94 patients received intravenous iron treatment and 224 patients received usual care. After excluding all factors possibly directly affecting Hb level, 52 and 153 patients remained in the IV and UC subgroup (figure 1).

Figure 1. Flow diagram



IV versus UC, total anemic cohort

An overview of the baseline characteristics is presented in table 1. Both groups had a mean age above 70 years (IV=71.8 ±11.1, UC=73.7 ±9.9, p=0.15). In the UC group, the majority was male as 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). Out 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 prior to iron infusion, while in 17 patients

Table 1. Patient baseline characteristics of all anemic patients at diagnosis, IV versus UC group

	IV group (n=94)	UC group (n=224)	p-value
Age (years mean, SD)	71.8 ± 11.1	73.7 ±9.9	0.15
Gender (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 localisation (%)			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			
timeframe			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
Hemoglobin (mmol/L)			
at diagnosis (mean, SD)	6.12 ±0.89	6.61 ±0.87	<0.001
Number patients with preop. BT (%) | Hb at diagnosis			<0.001
yes	30 (31.9) | 5.67 mmol/L	29 (12.9) | 5.56 mmol/L	
prior to iron infusion	13 | 5.68 mmol/L	NA	
after iron infusion	17 | 5.67 mmol/L	NA	
no	64 (68.1) | 6.32 mmol/L	195 (87.1) | 6.77 mmol/L	
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)	

Abbreviations: IV = intravenous iron group, UC = usual care group, BT = blood transfusion, preop. = preoperative, postop. = postoperative

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

	IV (n=52)	UC (n=153)	p-value
Characteristics			
Age (years mean, SD)	71.3 ± 11.6	74.3 ± 9.5	0.09
Gender (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 localisation (%)			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			
timeframe			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
Hemoglobin (mmol/L)			
at diagnosis (mean, SD)	6.3 ± 0.8	6.9 ±0.7	<0.001
Outcome			
Hemoglobin (mmol/L)			
increase diagnosis-preop. (mean, SD)	0.65 ±0.74	0.10 ±0.74	<0.001

Abbreviations: IV = intravenous iron group, UC = usual care group, preop. = preoperative

(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 1000-2000mg dose of iron(III)isomaltoside and iron(III)carboxymaltose, respectively. Both groups had a mean age above 70 years (IV=71.3 ±11.6, UC=74.3 ±9.5, p=0.09). In the UC group, more males were included as compared to the IV group (60.8% vs 44.2%, p=0.04) and there were more patients with a high ASA score (34% versus 19.2%, p=0.04). In the IV group, significantly more patients were operated

Table 3. Patient baseline characteristics high responder (=>0.6 mmol/L Hb increase) versus poor responder (<0.6 mmol/L Hb increase), receiving 1 dose iron infusion (1000mg)

	IV high responder (n=17)	IV poor responder (n=16)	p-value
Age (years mean, SD)	69.3 ±13.1	73.6 ±9.0	0.28
Gender (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 localisation (%)			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			
(median; IQR - mean ± SD)			
Hb (mmol/L)	6.0; 1.5 – 6.2 ±0.8	6.8; 1.1 – 6.6 ±0.7	
TSAT (%)	5.3; 4.6 – 7.3 ± 4.6	11; 15 – 16.3 ±14.3	
transferrin (g/L)	2.9; 0.4 – 3.1 ±0.5	2.7; 0.2 – 2.7 ±0.4	
ferritin (µg/L)	12; 27 – 36 ±52	27; 67 – 142 ±360	

Abbreviations: IV = intravenous iron group, TSAT = transferrin saturation

laparoscopically (82.7% vs 64.7%, p=0.02). Regarding comorbidity, tumor localisation 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 intravenous iron treatment showed a significant higher increase of Hb level as compared to patients with UC (IV=0.65 mmol/L vs UC=0.10 mmol/L, p<0.001). In identifying characteristics associated with Hb level response after iron infusion, patients receiving one dose of iron infusion (1000mg) were classified into high and poor responders. A cut-off 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, gender, ASA score, comorbidity, tumor localisation and tumor stage. Regarding iron status at diagnosis,

Table 4. Regression analysis on relationship between preoperative intravenous iron and postoperative blood transfusion in anemic patients (n=318)

	univariable			multivariable		
	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
Gender						
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 versus open	0.51	0.28 - 0.92	0.026	0.55	0.28 - 1.06	0.08
Tumor localisation						
rectum vs. colon	1.03	0.47 - 2.26	0.94	1.10	0.98 - 1.24	0.12
Timeframe 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 intravenous iron	**0.47**	**0.23 - 0.99**	**0.046**	**0.54**	**0.24 - 1.21**	**0.14**

high responders showed more distinct signs of anemia and iron deficiency as compared to poor responders (high versus poor responder, median values: Hb 6.0 mmol/L vs 6.8 mmol/L, transferrin saturation (TSAT) 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 intravenous iron therapy and postoperative complications and blood transfusions

All anemic patients, as presented in table 1, were included in logistic regression analyses. In univariable analysis, preoperative intravenous iron administration (OR=0.47, 95%CI 0.23 to 0.99, 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 to 1.21, p=0.14)(table

Table 5. Regression analysis on relationship between preoperative intravenous iron and postoperative complications in anemic patients (n=318)

	univariable			multivariable		
	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
Gender						
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 versus open	0.33	0.20 - 0.55	<0.001	0.32	0.18 - 0.55	<0.001
Tumor localisation						
rectum vs. colon	1.09	0.58 - 2.06	0.79	1.03	0.94 - 1.13	0.54
Timeframe 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 intravenous iron	**0.66**	**0.38 - 1.12**	**0.12**	**0.91**	**0.50 - 1.68**	**0.77**

4). In both uni- and multivariable analysis, no advantageous effect was found on postoperative complications (OR=0.66, 95% CI 0.28 to 1.12, p=0.12 and OR=0.91, 95%CI 0.50 to 1.68, p=0.77, respectively)(table 5).

DISCUSSION

The present study illustrates the efficacy of intravenous iron therapy in the optimisation of preoperative hemoglobin level in anemic colorectal cancer patients, as compared to usual care. We found that intravenous 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, as compared to functional iron deficiency. In present 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 generalised.

Our results add to a growing body of evidence in the literature demonstrating the efficacy of preoperative intravenous iron therapy in colorectal cancer patients, and contribute to the ongoing debate whether preoperative intravenous iron therapy is improving postoperative outcome. Our results are consistent with the results of a prospective randomised trial by Keeler et al., comparing the effect of preoperative oral versus intravenous iron in anemic colorectal cancer patients.24 No overall benefit was seen with intravenous iron in reducing blood transfusions and postoperative complications, despite the fact that in the study by Keeler et al. oral iron administration represented usual care. However, in addition to the study by Keeler et al., we also identified patients characteristics associated with hemoglobin level response after iron infusion. Evidently, higher transferrin and lower ferritin levels, markers for absolute iron deficiency, were associated with a higher hemoglobin level response after iron infusion. Increased ferritin level, a marker for functional iron deficiency, could be the cause of poor hemoglobin level response after iron infusion. In this respect, increased uptake and retention of the administered intravenous 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 iron deficiency and emphasize the efficacy of intravenous iron namely in patients with absolute iron deficiency. It is noteworthy that in present international guidelines on the treatment of anemia in oncological patients a distinction between type of iron deficiency is already made: intravenous 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 iron deficiency. Ongoing and future randomised clinical trials have to establish whether the optimisation of preoperative hemoglobin level by preoperative intravenous iron therapy is resulting in improved postoperative outcome.[11, 13]

STRENGTH AND LIMITATIONS

A key strength of our study is the identification of patient characteristics associated with hemoglobin 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 iron deficiency in the treatment of preoperative anemia not only with oral iron but even with intravenous iron.

The main limitations of our study are three-fold, 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 intravenous iron and usual care group (e.g. baseline hemoglobin levels and timeframe 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. The past years, great efforts have been made to optimise the results of colorectal cancer surgery. In addition to surgical techniques and procedures[9, 10, 27], also blood transfusion strategy, as part of patient blood management (PBM), has 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. Presently, a restrictive transfusion threshold is recommended for hospitalised adult patients and seems to be safe in the oncological setting.[28, 29] Moreover, standard-issue RBC units rather than fresh RBC units (storage length: <10 days), and, to initiate, one rather than two RBC units are advised.[29] Although we corrected our results for the year of treatment, the combined efforts to optimise colorectal cancer care (e.g. centralisation, protocols, laparoscopy) might have contributed differently to the results. This emphasises the importance of performing a randomised controlled trial comparing usual care (i.e. no therapy or oral iron) with intravenous iron supplementation in colorectal cancer patients, in which, importantly, intravenous iron has to be administered as early as possibly, preferably at least three weeks prior to surgery for its optimal effect[11].

Second, this study focused specifically on preoperative treatment of anemia . However, investigation and treatment of merely hemoglobin levels appears to be a suboptimal way to indicate overall performance and therefore, presently, 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 percent is observed.[32, 33] In line with the previous limitation, in present study, various multimodal programs may similarly introduce confounding of our results that are not easily corrected for. A randomised trial could correct for both continuing pre- as well as postoperative care optimisation.

The third limitation was that only short-term effects of intravenous 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 that exposure to iron to be a risk factor for developing colorectal cancer and tumor growth.[35, 36] In this regard, intraluminal colorectal tumours might be more affected by oral iron administration, while intravenous iron with a higher risk of non-transferrin bound serum iron and reactive oxygen species presence might also influence systemic tumor growth. Randomised 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.

CONCLUSION

We were able to show that implementation of intravenous iron therapy leads to optimisation of preoperative hemoglobin level. Furthermore, we showed the importance of assessing the type of iron deficiency. Iron infusion is most effective in patients with more severe anemia and with higher transferrin and lower ferritin levels, markers for absolute iron deficiency, as compared to functional iron deficiency. Following the optimisation of preoperative hemoglobin level, strikingly, no significant decrease in the percentage of patients with a postoperative blood transfusion and postoperative complication were observed. However, from present cohort study, due to its retrospective nature, we cannot entirely conclude that intravenous iron and the associated Hb increase does decrease the postoperative blood transfusion and complication rate. Future randomised trials are thus required to not only establish the short-term benefits, but also the potential long-term hazards of preoperative intravenous iron therapy in colorectal cancer patients.

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