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Original Article

The Multidisciplinary Approach is Useful for Optimising Preoperative Haemoglobin in Colorectal Cancer Surgery

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A B S T R A C T

Introduction: Optimising haemoglobin (Hb) levels less than 13 g/dl in the preoperative period can reduce the transfusion rate. With this aim, we developed a multidisciplinary protocol in our hospital for the treatment of patients proposed for colorectal cancer surgery.
Patients and method: A study was conducted on 437 patients who had surgery performed for colorectal cancer in the period 2005-2009. The data recorded were: demographic data, Hb and iron metabolism (Fe) at the time of diagnosis, Hb on the day of the surgery and on discharge, tumour location, preoperative adjuvant treatment (chemotherapy and/or radiotherapy), tumour stage (TNM), iron treatment, transfusion rate, and complications at 30 days. Patients were classified into Group A; Hb<13 g/dl and/or abnormal Fe metabolism, and Group B; Hb>13 g/dl and/or normal Fe metabolism.
Results: Of the total, 53.3% were in Group B and were treated with Fe; 73.6% intravenous (IV), and the rest oral. The mean dose of IV Fe was 867 mg. The mean intraindividual difference between the Hb on the day of surgery and at the initial value, increased by 0.6 g/dl in Group A, while it decreased by 0.8 g/dl in Group B. The mean intraindividual difference between the Hb at discharge and the diagnosis decreased by 0.4 g/dl in Group A compared to 2.5 g/dl in Group B. The overall transfusion rate was 8.6%. No statistically significant differences were observed in complications.
Conclusions: A multidisciplinary and early treatment of colorectal cancer enables patients with a low haemoglobin (Group A) to be optimised, as well as achieving a lower transfusion rate.

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El abordaje multidisciplinar es útil para la optimizacón de la hemoglobina preoperatoria en cirugía neoplásica colorrectal

Palabras clave:
Anemia
Hierro intravenoso
Tasa transfusional
Cáncer colorrectal

R E S U M E N

Introducción: La optimización de la hemoglobina (Hb) inferior a 13 g/dl en el preoperatorio puede disminuir la transfusión. Con este objetivo se puso en marcha en nuestro centro un protocolo multidisciplinar destinado al tratamiento de pacientes propuestos para cirugía neoplásica colorrectal.

Pacientes y método: Se estudiaron prospectivamente 437 pacientes intervenidos de neoplasia colorrectal desde 2005 hasta 2009. Se registraron: datos demográficos, Hb y metabolismo de hierro (Fe) en el momento del diagnóstico, Hb el día de la cirugía y al alta hospitalaria, localización tumoral, tratamiento adyuvante preoperatorio (quimio- y/o radioterapia), estadio tumoral (TNM), tratamiento con Fe, tasa transfusional y complicaciones a los 30 días. Los pacientes se clasificaron en grupo A: Hb < 13 g/dl y/o metabolismo de Fe alterado y grupo B, Hb > 13 g/dl y/o metabolismo de Fe normal.

Resultados: El 53,3% de los pacientes pertenecían al grupo A y fueron tratados con Fe: 73,6% intravenoso (IV), el resto oral. Dosis media de Fe IV: 867 mg. La media de las diferencias intrasujeto entre la Hb del día de la cirugía y la inicial aumentó 0,6 g/dl en el grupo A, mientras que en el grupo B disminuyó 0,8 g/dl. La media de las diferencias intrasujeto entre la Hb al alta y del diagnóstico descendió 0,4 g/dl en el grupo A vs. 2,5 g/dl en el grupo B. Tasa transfusional global: 8,6%. No se encontraron diferencias estadísticamente significativas en las complicaciones.

Conclusiones: El abordaje multidisciplinar y precoz de la neoplasia de colon permitió la optimización de los pacientes del grupo A, así como alcanzar una tasa transfusional baja.

Introduction

Anaemia is one of the main symptoms of colorectal cancer. The incidence is high depending on the haemoglobin (Hb) value, age, tumour location and stage.[1] Anaemia associated with this type of cancer can be for various reasons, not only blood loss but also the cytokine-mediated inflammatory response secondary to malignant disease, which interferes with erythropoiesis, reducing the availability of iron (Fe) for bone marrow.[2]

Also, it is well established that preoperative anaemia is associated with a higher requirement for allogeneic blood transfusion (ABT) in the perioperative management of colorectal cancer, reaching figures of 20%-85%,[3] which exposes patients to a significantly increased rate of postoperative infection and tumour recurrence.[4,5] It is therefore recommended to reduce ABT to the minimum required level. Correction of anaemia with iron may be a strategy. It is known that oral iron treatment is not indicated for this type of surgical patients. Due to the effect of the hormone hepcidin, a key regulator in iron metabolism, intestinal absorption and mobilisation of iron deposits from macrophages are deeply inhibited, which explains the ineffectiveness of oral iron therapy.[3,6-8] However, intravenous (IV) administration of iron is an effective and safe therapeutic measure to correct anaemia, due to the more rapid and prolonged erythropoietic response, as such it is a clinically proven alternative to blood transfusions.[9-12]

In 2005, the *Departamento de Salud de la Generalitat de Catalunya* (Catalonia Government Health Department) established a rapid diagnosis programme for the most prevalent types of cancer, including colorectal cancer, to reduce the delay between the suspicion of cancer, diagnosis and treatment. Our centre was one of the 7 participating hospitals. A multidisciplinary team agreed on an in-patient protocol describing the procedure from the time a patient had signs of suspected colon cancer. This established a strategy for optimising preoperative Hb, considering a systematic evaluation by a multidisciplinary group in the context of a clinical protocol can offer the patient a better chance of recovery.[13]

The main objective of the study was to analyse the results of implementing a multidisciplinary protocol in our centre, which was agreed by the departments involved (Digestive System Endoscopy, General and Digestive System Surgery, Anaesthesiology, Haematology and Oncology) for optimising preoperative Hb in patients undergoing colorectal neoplastic surgery.

Patients and Method

Study Design and Patients

This was a descriptive, prospective, longitudinal study approved by the Research Ethics Committee (CEIC 2005527) for patients diagnosed with colorectal neoplasia from 2005 to 2009 in the catchment area of the Hospital de Sabadell, comprising 421 077 inhabitants.

Inclusion criteria: all patients over 18 diagnosed with colon cancer and with scheduled radical surgery.

Exclusion criteria: acute or chronic infection, iron overload, history of hypersensitivity to parenteral iron preparations, emergency surgery and the presence of distant metastasis.

Variables Recorded

Demographic data (age, sex, ASA score and hospital stay); Hb and iron metabolism (serum iron, transferrin, ferritin and transferrin saturation) at the time of diagnosis; tumour location; tumour stage; preoperative adjuvant therapy (chemotherapy and/or radiotherapy); treatment with IV or oral iron; Hb on the day of surgery and at discharge; iron treatment duration; transfusion and complication rate 30 days after surgery.

Procedure

A colonoscopy was performed if colonic neoplasia was suspected. If this was positive, the patient was included in the specific optimisation procedure (Figure 1). A coloproctology visit was scheduled with an analysis that included a haemogram, iron metabolism, biochemical and nutritional parameters and tumour markers. The relevant anaesthesiologist evaluated the analytical results. If Hb<13 g/dl and/or iron metabolism was altered, the patient was referred to the Haematology department for iron treatment (Group A). Patients who could go to the hospital were administered IV iron to compensate for the total iron deficit (TID), calculated according to the formula: TID (mg) = [(2.4 × body weight × (Hb final – Hb initial)] + 500. On an outpatient basis, IV iron was administered at a dose of 200 mg every 48 hours. Those unable to go to the hospital received oral iron until the surgery. Patients with Hb>13 g/dl were classified in Group B.

Parallel to the optimisation, an extension study was also performed (using CT, MRI, etc.), as well as adjuvant therapy if they were candidates and a preoperative anaesthetic visit. Patients underwent a Hb test just before surgery. In the immediate postoperative period, all patients received 200 mg of IV iron in the post-anaesthesia care unit. A transfusion during hospitalisation was indicated for Hb<8 g/dl or anaemic syndrome, following the hospital transfusion guidelines. Another Hb test was performed at hospital discharge. Patients were evaluated by the surgery unit in a follow-up visit one month after surgery. Any complications during the first 30 postoperative days were recorded.

Statistical Analysis

A descriptive statistics analysis was performed. Continuous variables were expressed as mean and 95% confidence interval (CI), while qualitative variables were expressed as absolute frequencies. A within-patient analysis assessed the changes in haemoglobin (g/dl) values for groups A and B (at

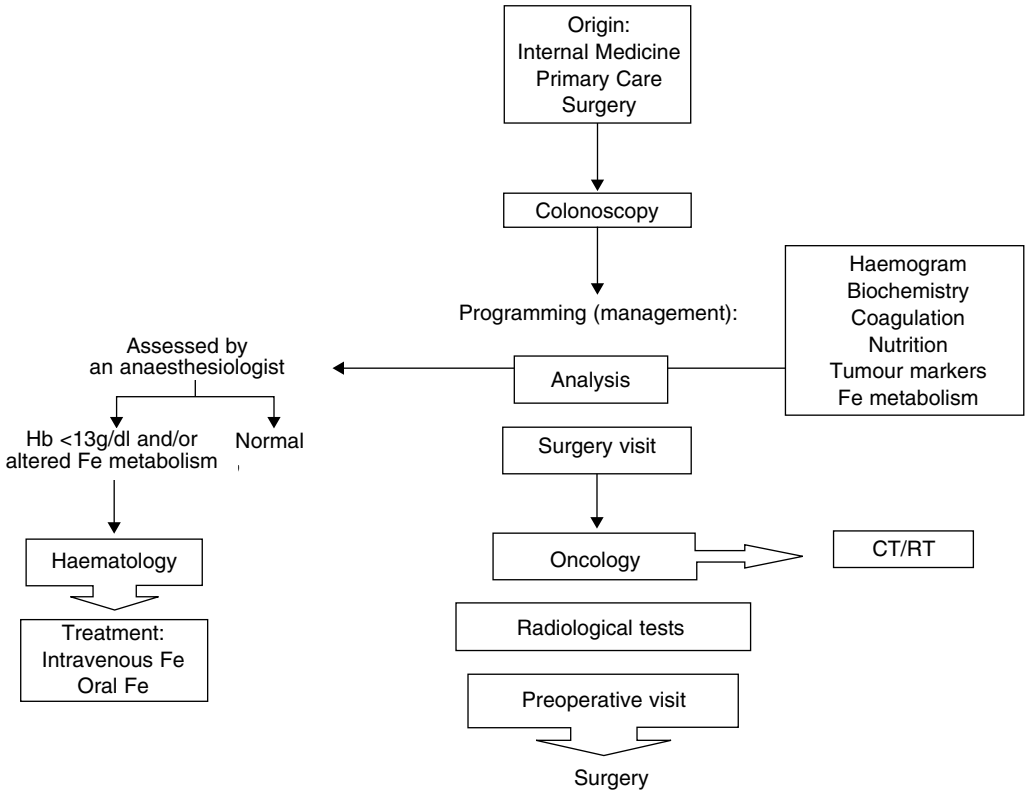

Figure 1 – Optimisation procedure for patients with suspected colon cancer.

diagnosis, day of surgery and discharge), and Student's t tests were used for paired data. The significance level was set at $P<.05$ for all tests. Data collection was performed using an Access database, Microsoft Office 2003. The calculations were performed using the SPSS statistical program, version 17.0.

Results

The total number of patients included in the optimisation procedure during the study period was 643. Figure 2 shows the patient distribution chart. Patients excluded from the study were also treated if they had a Hb<13 g/dl, considering that all patients with an iron deficiency may benefit from iron treatment

The final study sample was 437 patients.

Demographic data and patient characteristics are shown in Table 1.

There were more males (70.2%) than females in Group A.

Most patients in both groups were ASA II.

At the time of diagnosis, 242 patients (53.3%) had Hb<13 g/dl and/or altered iron metabolism.

Tumour stage II was the most frequent stage for both groups.

Most patients (73.6%) received intravenous iron.

The most common tumour location in patients was the rectum (168 patients, see Figure 3).

Preoperative neoadjuvant treatment was administered to 96 patients with rectal cancer (52.7%).

The average total dose received was 867 mg of IV iron (95% CI: 793.7-940.2).

The evolution of the mean Hb in both groups from diagnosis to hospital discharge is shown in Table 2. The within-patient analysis showed that the Hb value from diagnosis to the day of surgery increased by 62.4% for patients in Group A, compared to 10.3% in Group B. In Group A there was a statistically significant average increase of 0.6 g/dl (95% CI: 0.4-0.7), while Group B showed an average statistically significant decrease of 0.8 g/dl (95% CI: 0.7-0.9). The mean Hb values from diagnosis to discharge in Group A decreased by 0.4 g/dl (95% CI: 0.2-0.6), while in Group B the decrease was of 2.5 mg/dl (95% CI: 2.3 to 2.7); both results were statistically significant.

The iron treatment duration in patients not undergoing neoadjuvant therapy was 28.4 days (range 2-90) from diagnosis to surgery, while for those who did receive the therapy was 20.7 (range 6-66) from diagnosis to the start of neoadjuvant therapy.

The overall transfusion rate was 8.6% (38 patients), and it was higher in Group A (32 patients). Most of them were ASA III-IV, with tumour stage II-III and right colon location. Of the total transfused patients in this group, 3 had received neoadjuvant treatment. There were 11 cases of postoperative infections among those transfused in this group and 14 surgical complications (Table 3).

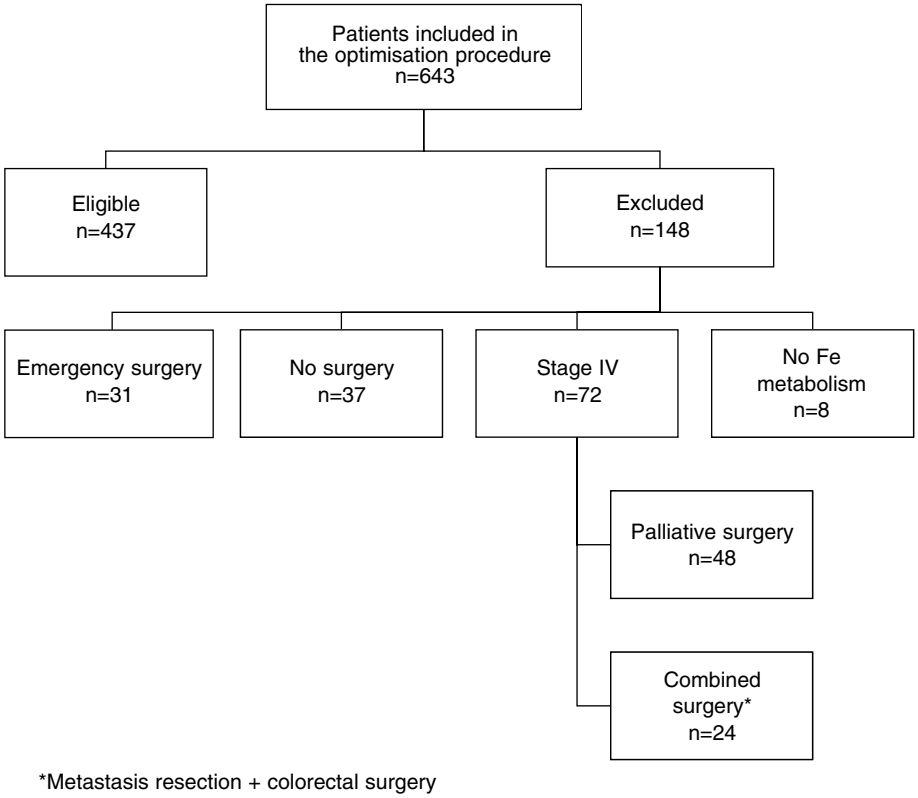

Figure 2 – Chart.

Table 1 – Characteristics of Patients Admitted for Scheduled Colorectal Surgery in the Study.

	Group A n=242	Group B n=195	P
Age, years, X (CI: 95%)	65.4 (63.7-66.9)	69.9 (68.5-71.3)	<.05
Males, no. (%)	116 (47.9)	137 (70.2)	<.05
Stay, days, X (CI: 95%)	13.7 (12.6-14.8)	12.8 (11.7-13.9)	.28
ASA score, n			<.05
II	129	134	
III	104	57	
IV	9	4	
Hb at diagnosis, g/dl	10.9 (10.7-11.1)	14.3 (14.1-14.4)	<.05
Fe metabolism at diagnosis:			
Iron, µg/dl	41.5 (37.8-45.3)	72.4 (68.2-76.3)	.10
Ferritin, ng/dl	71.6 (57.4-85.7)	107.2 (89.3-125)	.17
Transferrin, mg/dl	271.7 (264.5-278.8)	260.3 (253.5-267)	.01
Transferrin saturation, %	9.5 (8.5-10.4)	16.2 (15-17.4)	.05
Tumour stage (n)			.196
I	46	51	
II	98	70	
III	98	74	
Treatment no., %			
IV iron (before surgery)	178 (73.6)	-	
Oral iron	64 (26.4)	-	
Adjuvant (CT and/or RT)	44 (18.2)	52 (21.5)	.97
IV Fe, mg, X (CI: 95%)	867 (793.7-940.2)	-	

CI indicates confidence interval; CT, chemotherapy; Fe, iron; Hb, haemoglobin; no., number of patients; RT, radiotherapy; X, mean.

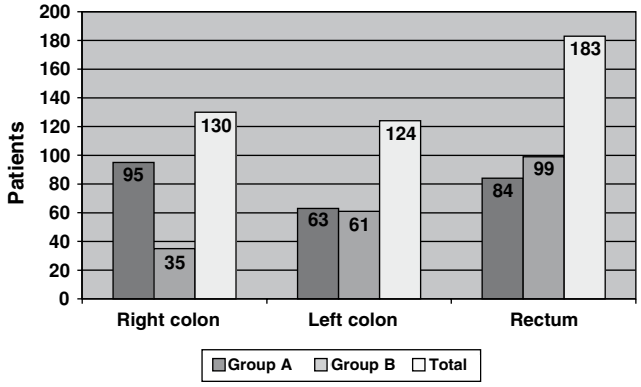

Figure 3 – Distribution according to tumour location.

Complications 30 days after surgery are shown in Table 4. The most common in Group A were paralytic ileus, surgical wound infection and dehiscence of anastomosis; while in Group B it was paralytic ileus, surgical wound infection and renal failure.

Discussion

After 5 years of implementing the rapid diagnosis protocol for colon cancer with a strategy to optimise preoperative Hb conducted by a multidisciplinary team, 73.6% of patients who had pre-operative Hb<13 g/dl were treated with IV iron before surgery, which led to an overall transfusion rate of 8.6%.

Numerous studies have described the high incidence of anaemia in colon cancer. In our study, 53.3% had Hb<13 g/dl and/or altered Fe metabolism at the time of diagnosis, with the right colon being the most common location in these cases. These results are consistent with the literature.[1]

Preoperative treatment of anaemia has been proven an effective and safe treatment, provided the doses administered replace the total iron deficit and that the

Table 2 – Evolution of the Mean Hb Values.

	Group A, n=242	Group B, n=195	P
Diagnosis, g/dl (CI: 95%)	10.9 (10.7-11.1)	14.3 (14.1-14.4)	<.05
Day of surgery	11.5 (11.3-11.7)	13.5 (13.3-13.7)	.118
Discharge	10.5 (10.4-10.7)	11.8 (11.5-12)	.60

Table 3 – Characteristics of Transfused Patients in Group A.

	n=32	Total=242
Sex, n		
Male	15	116
Female	17	126
ASA		
II	8	129
III	21	104
IV	3	9
Tumour stage		
I	5	46
II	15	98
III	12	98
Adjuvant treatment	3	44
Tumour location		
Right colon	15	80
Left colon	7	56
Rectum	10	74
Complications		
Infections	11	55
Surgical	14	58
Non-surgical	6	26

response time required for erythropoiesis is sufficient for proper filling of the deposits. Muñoz et al assessed the effectiveness of preoperative administration of intravenous iron (mean=1000 mg) in anaemic patients referred for neoplastic colon surgery 3-5 weeks before surgery, and found an average increase of 2 g/dl in the Hb value.[12] However, Edwards et al administered 600 mg of IV iron to a group of patients undergoing colorectal neoplasm 14 days before surgery and saw no significant differences from placebo in the Hb values and the transfusion rate.[14] This may be because the administered dose was insufficient and the period for observing a change in Hb value was less than 2-4 weeks, which is the time required for a positive response (increase of Hb>2 g/dl).[7] In our study, an average dose of 867 mg of IV iron was sufficient to increase the Hb value in 62.4% of patients who were optimised. No patient discontinued treatment with iron before surgery due to normalisation of Hb. Noting how the Hb value evolved, there was an increase of 0.6 g/dl in Group A during the diagnosis-surgery period. In Group B, the tendency was downward from the moment of diagnosis to hospital discharge (2.5 g/dl). This tendency to progressive anaemia observed in both groups, secondary to neoplastic disorder, chemo-radiotherapy treatment, the blood loss due to the tumour and later surgery, could demonstrate that if the Group A patients had not been treated by refilling the Fe deposits, haemoglobin levels would have reached undesirably low levels.

Furthermore, patients who were not optimised would also probably have benefited from treatment with IV iron.

Although some authors have treated these patients with oral iron and observed an increase in Hb and a decrease in transfusions after treatment for 2 weeks before surgery,[15,16] preoperative treatment of anaemia with oral iron requires 1-4 months to achieve a normalisation of Hb levels.[8] Despite knowing the limitations, we chose to treat patients who had no chance of getting to the hospital for a parenteral treatment with oral iron. Another possibility would have been a single high dose of IV iron, but this presentation was not available in our centre.

In a recent epidemiological study by a group of 39 Spanish hospitals, it was observed that there was time available to optimise anaemia, as the length of time that elapsed from the time of diagnosis with malignancy to surgery was approximately 6 weeks.[11] In our study, Group A patients were treated for an average of 28 days if they underwent no neoadjuvant therapy, and there was no delay in surgery in any of the cases. Although no patient was able to completely replace their iron deposits, it was observed that the tendency to anaemia in Group B did not occur in patients treated with iron, which could be attributed to patient iron deposits being restored during treatment.

In recent years, there has been controversy regarding preoperative administration of erythropoietin and intravenous iron in anaemic patients undergoing neoplastic surgery. In a Cochrane review published in 2009, Devon et al concluded that there was insufficient evidence to recommend the use of erythropoiesis-stimulating agents in perioperative neoplastic colorectal surgery to improve anaemia and reduce transfusions.[17] No patient in our study was administered erythropoietin due to the recent controversy in this field.

The rate of perioperative transfusions for colorectal cancer surgery reaches undesirably high rates. In the aforementioned

Table 4 – Postoperative Complications.

	Group A n=242	Group B n=195
Infections		
Surgical wound infection	31	32
Intra-abdominal abscess	5	9
Anastomotic dehiscence	25	9
Catheter	1	2
Urinary	10	9
Respiratory	2	2
Surgical		
Haematoma	2	3
Wound bleeding	-	3
Evisceration	6	3
Gastrointestinal bleeding	3	3
Haemoperitoneum	1	3
Intestinal fistula	1	-
Paralytic ileus	34	36
Mechanical ileus	2	2
Non-Surgical		
Respiratory	10	12
Cardiovascular	6	5
Uro-nephrology	17	20
Neurological	2	-

Spanish epidemiological study,[11] nearly 15% of patients with colon neoplasia received preoperative blood transfusions, reaching almost 25% when the cancer was located in the rectum. The Spanish Rodriguez-Cuellar study, which analysed the quality of colorectal cancer surgical treatment care in 15 regions, found a transfusion rate of 20.6%.[18] The global transfusion rate for patients in our study was 8.6%, and no patients underwent a transfusion in the preoperative or intraoperative period. Iron treatment allowed patients to maintain Hb levels above the institutional transfusion guide threshold.

The vast majority of patients who required a transfusion belonged to Group A. Because only a few cases were transfused in the same treated group, it is difficult to compare them. In Group B, only 6 patients were transfused.

Therefore, with such a low rate of transfused patients it is difficult to draw conclusions. It was observed that most of them were patients who had undergone rectum surgery (whose losses are greater than in the other colon surgery procedures) or patients with the tumour located in the right colon, which often leads to a greater degree of anaemia.

Transfused patients were mostly ASA III-IV. If they had received higher iron doses in the preoperative period, they probably would have been better optimised for surgery. The transfusion was not associated with advanced tumour stages.

Furthermore, patients who received adjuvant therapy did not need more transfusions, with only 5 of the 96 patients who received chemotherapy and/or radiotherapy being transfused.

Study Limitations

Firstly, not comparing optimised patients with a control group prevents any conclusions being drawn about the transfusion rate decreasing. It is standard practice in our centre to treat patients with iron deficiency before neoplastic colorectal surgery, therefore we did not consider it ethical to stop treating patients that would certainly benefit from this treatment.

Many patients could not receive the full TID due to lack of time. Fewer transfusions would probably have been required if the biological iron deposits had been able to be filled before surgery.

Another limitation was the difficulty in collecting analytical data after surgery, which was why a significant number of patients had to be excluded. Also, the Hb and iron metabolism values were not followed up after the adjuvant treatment that candidate patients received.

In conclusion, despite these limitations, we believe that the results of this study indicate that a multidisciplinary and early approach to colon cancer improves Hb levels and/or iron metabolism alterations, which leads to a lower perioperative transfusion rate.

Conflict of Interest

The authors affirm they have no conflict of interest.

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