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Epidemiological study of preoperative anaemia in surgical oncology patients in spain. RECIRON study

Lourdes Durán,[a,b,*] *Victoria Moral,*[a,c] *Misericordia Basora,*[a,d] *María José Colomina,*[a,e] *Juan Vicente Llau,*[a,f] *Calixto Andrés Sánchez,*[a,g] *Sonsoles Silva,*[a,h] *and Miguel Vila*[a,i]

[a]*Grupo de Estudio para el Ahorro de Sangre (GEAS)*
[b]*Servicio de Anestesiología y Reanimación, Hospital Clínico San Carlos, Madrid, Spain*
[c]*Servicio de Anestesiología y Reanimación, Hospital de la Santa Creu i Sant Pau, Barcelona, Spain*
[d]*Servicio de Anestesiología y Reanimación, Hospital Clínic, Barcelona, Spain*
[e]*Servicio de Anestesiología y Reanimación, Hospital Vall d'Hebron, Barcelona, Spain*
[f]*Servicio de Anestesiología y Reanimación, Hospital Clínico, Valencia, Spain*
[g]*Servicio de Anestesiología y Reanimación, Hospital General de Elda, Alicante, Spain*
h*Servicio de Anestesiología y Reanimación, Hospital General Insular, Las Palmas de Gran Canaria, Las Palmas, Spain*
[i]*Servicio de Anestesiología y Reanimación, Hospital General de Castellón, Castellón, Spain*

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A B S T R A C T

Introduction: Anaemia is common in oncology patients who are going to have surgery for tumour resection. Allogenic blood transfusion has been associated with a greater incidence of postoperative complications. The aim of this study is to analyse current clinical practice as regards the preoperative treatment and conditions of these patients in Spain.

Material and method: This is an epidemiological observational study which included 472 patients from different hospitals. The data included in the clinical history was analysed: tumour location, preoperative laboratory tests, functional situation (Karnofsky index [KI]), anaemia treatment, and transfusions given since the diagnosis.

Results: As regards the tumour location, 181 were urological (38.3%), 161 digestive system (34.1%), and 130 gynaecological (27.5%). The time from the initial diagnosis until surgical intervention was 6.2 (6) weeks, and 19.1 (23) days from the anaesthetist visit to the surgical operation. The mean pre-operative haemoglobin (Hb) was 13.1 (2) g/dL. The anaemia was treated in 12.9% of the patients and 15% (69 patients) received a transfusion before surgery. A total of 28.1% patients had a KI ≤80. The lowest preoperative haemoglobin levels are associated with the lowest KI.

Conclusions: Anaemia is present in a high percentage of oncology patients who are going to be surgically treated. Preoperative blood transfusion is the most common treatment. It was observed that there is sufficient preoperative time to be able to improve preparation of the patient for surgery.

*Author for correspondence.
E-mail address: ldurangi38@hotmail.com (L. Durán).

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Estudio epidemiológico de la anemia preoperatoria en pacientes sometidos a cirugía oncológica en España. Estudio RECIRON

R E S U M E N

Introducción: La anemia es frecuente en el paciente oncológico que va a ser sometido a cirugía para resección tumoral. La transfusión de sangre alogénica se ha relacionado con una mayor incidencia de complicaciones postoperatorias. El objetivo de este estudio es analizar la práctica clínica actual en relación con el tratamiento y las condiciones preoperatorias de estos pacientes en nuestro medio.

Material y método: Se trata de un estudio observacional epidemiológico en el que se incluye a 472 pacientes procedentes de distintos hospitales. Se analizan los datos incluidos en la historia clínica: Localización tumoral, analítica preoperatoria, situación funcional (índice de Karnofsky [IK]), tratamiento de la anemia y transfusiones realizadas desde el diagnóstico.

Resultados: Según la localización tumoral, hay 181 tumores urológicos (38,3%), 161 digestivos (34,1%) y 130 ginecológicos (27,5%). El tiempo transcurrido desde el momento del diagnóstico hasta la intervención quirúrgica fue de 6,2 ± 6 semanas, y 19,1 ± 23 días desde la consulta de preanestesia hasta la intervención quirúrgica. La hemoglobina (Hb) preoperatoria media fue 13,1 ± 2 g/dl. En el 12,9% de los pacientes se trató la anemia y un 15% (69 pacientes) recibió alguna transfusión antes de la cirugía. El 28,1% de los pacientes presentaban un IK ≤ 80. Las cifras preoperatorias de Hb más bajas se relacionan con los IK más bajos.

Conclusiones: Un porcentaje elevado de pacientes oncológicos que van a ser tratados quirúrgicamente tienen anemia. La transfusión de sangre preoperatoria es el tratamiento más frecuente. Se observa que hay un tiempo preoperatorio suficiente que permitiría mejorar la preparación del paciente para la intervención quirúrgica.

Introduction

Although there has been a significant decrease in the use of allogenic blood transfusions (ABT) during the last years, the perioperative administration of blood derivates is relatively common in oncological patients undergoing surgery. However, transfusional practice differs greatly among the different hospitals. Blumberg et al,[1] describe in their meta-analysis a transfusional rate of 45%-78%, whereas Nilsson et al[2] situate this rate at 3%-31% of the 14 052 patients undergoing surgery for colorectal cancer in 1994-2000. The ABT in oncological patients is associated to especially relevant risks, from which stands out allogenic transfusion-induced immunomodulation (ATII) that could be related to a worse clinical prognosis, an increase in postoperative infections and/or higher incidence of tumour recurrence.[3-5]

On the other hand, anaemia is the most common alteration in neoplasic patients. Its prevalence is determined by the type of disease and its treatment.[6] This is generally moderate anaemia, although 15%-23% of patients with solid tumours require transfusions at some time during their evolution.[7] To prevent or minimise the essential use of ABT and reduce any adverse effects as far as possible that the tumour might have on the neoplasic patient, a well-defined perioperative blood saving strategy is required. Any saving measures must take place prior to carrying out an adequate anamnesis that enables the preoperative preparation of the patient to be optimised.

Given that in Spain there is a lack of detailed information on the biological situation of the oncological patients programmed for elective cancer surgery, the purpose of this study is to gain more thorough knowledge of this population that enables risk factors to be evaluated and a more in-depth knowledge to be obtained regarding the appropriate management of transfusional alternatives for these patients.

Material and Method

This is an observational epidemiological, cross-cutting, prospective, multi-centre study in which 39 Spanish hospital centres participated.

The inclusion period for the patients was 1 week. Each centre included all the patients undergoing surgery in the week of the study who complied with the inclusion criteria: patients diagnosed with digestive, urological, or gynaecological tumours undergoing scheduled surgery for tumour resection in the week of the study (July 2005) who had signed the informed consent. As this was a record type study, there was no pre-determined number. The variables recorded and compiled in the patients' medical records, were the following: demographic data (age and sex), data relating to the oncological disease (location of tumour, interval between the diagnosis and the date of the surgical intervention, interval between the pre-anaesthetic consultation and the surgical intervention, treatments prior to chemotherapy and/or radiotherapy and clinical stage, functional clinical

Table 1. Tumour Location

Digestive		Urology		Gynaecology	
Localisation	No.	Localisation	No.	Localisation	No.
Colon	58	Bladder	105	Breast	86
Rectum	37	Prostate	47	Uterus	29
Stomach	22	Kidney	23	Ovary	12
Liver	13	Urinary tract	3	Pelvis	2
Pancreas	11	Testicle	3	Vagina	1
Oesophagus	7				
Bile duct	4				
Gall bladder	2				
Duodenum	1				
Small intestine	1				
Retroperitoneum	3				
Peritoneum	2				
Total	161		181		130

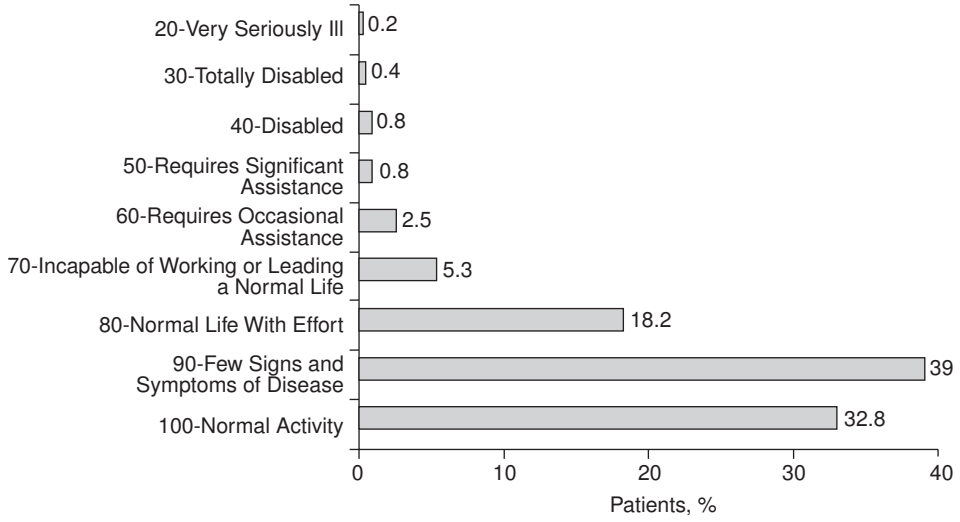

Figure 1 – Functional status. Evaluation according to the Karnofsky scale.

status evaluated according to the Karnofsky Index [KI]), data relating to biological parameters or pre-operative analytical tests (haemoglobin, iron metabolism, proteinogram, and liver function tests), data relating to preoperative transfusions (transfusion since the diagnosis of the oncological disease and transfusion in the month before the intervention), and data relating to the treatment of anaemia (whether currently treated with iron, folic acid and/or vitamin B_{12}, and erythropoiesis stimulating agents).

Statistical Analysis

The absolute and relative distributions of the qualitative variables are presented, as well as the central trend measures and dispersion of the quantitative variables. The SPSS Version 13.0 software was used to perform the analysis.

Results

A total of 492 patients were recruited during the study period, 20 of which being excluded due to different causes (including incorrect diagnosis in 7 cases; inclusion outside the period in 1 case; incomplete data in 12 cases). The effective sample in the study was, therefore, 472 patients: 261 men (55.3%) and 211 women (44.7%); the mean age was 65.6 (13) years.

A total of 83.5% of the tumours were primary and the distribution by tumour location was as follows: 38.3% (n=181), urological; 34.1% (n=161), digestive; and 27.5% (n=130), gynaecological. Very common locations were the bladder (22.2%), breast (18.2%), and colon (12.3%) (Table 1).

A total of 36 (7.6%) cases had previously been treated with chemotherapy and 7 (1.5%) with radiotherapy. Also, 10 (2.1%) patients had received combined chemotherapy and

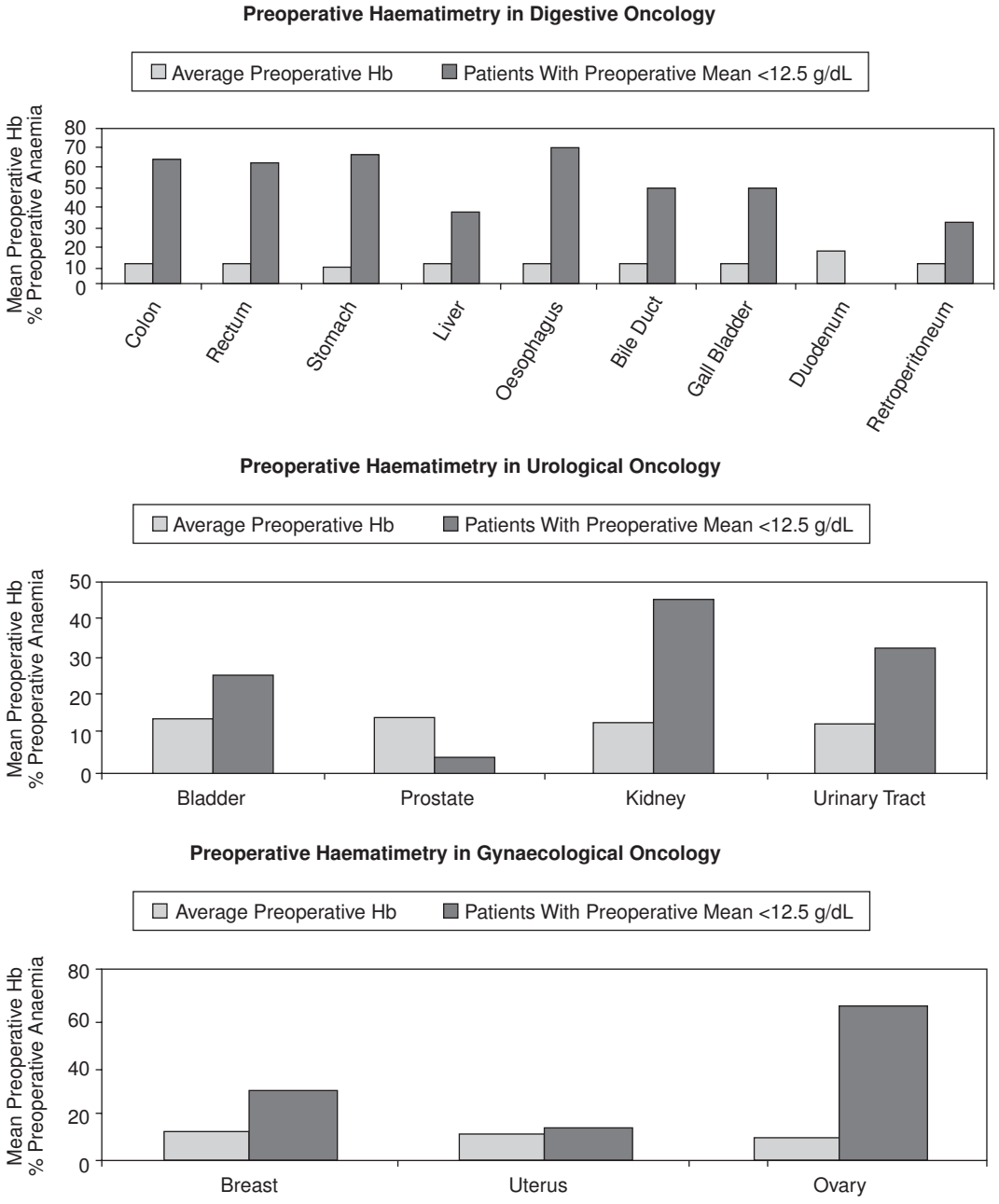

Figure 2 – Preoperative haematimetric values.

radiotherapy. The total patients with chemotherapy prior to surgery was 46 (9.7%), and the total patients previously treated with radiotherapy was 17 (3.6%); 419 patients did not receive any treatment prior to the surgery.

Seventy-one point eight percent of the patients presented a KI >80 and 28.1% ≤80 (Figure 1).

The time between the diagnoses until the date of the surgery was 6.2 (6) weeks and the time between the pre-anaesthetic visit and the surgery was 19.1 (23) days.

The mean preoperative haemoglobin (Hb) value was 13.1 (2) g/dL and 44.2% of the patients had lower figures. Analysing the mean Hb levels obtained according to the tumour location, it was seen that the lowest values corresponded to tumours in the gastrointestinal tract. A total of 49% of patients with primary digestive tumours had presurgical values of Hb <12.5 g/dL, especially the patient candidates for oncological surgery of the oesophagus, stomach, colon and rectum (Figure 2).

The relationship of the KI with the mean value of presurgical Hb showed that the lowest were found in the group of patients with KI 30-70, which presented an average of preoperative Hb of 11.9 (2 g/dL). For KI = 80, the preoperative

Hb was 12.2 (2) g/dL. Analysing the subpopulations of KI 30-80 according to tumour location, the digestive tumours were those that presented the lowest mean values of preoperative Hb (Figure 3).

The study of the biological preoperative parameters of the iron metabolism and the level of systemic inflammatory reaction have been practised in a disperse manner and in an insufficient number of patients (n<80), meaning the data is extremely disperse, which hinders its evaluation (Table 2).

A total of 8.9% of the patients in our study received preoperative ABT, more frequently in digestive oncological surgery (19.9%) than in urological or gynaecological oncological surgery (4.4% and 1.5% respectively). The least frequent tumour locations with higher frequency of preoperative ABT were the stomach, rectum, liver, and bile duct (Figure 4). The average transfusions from diagnosis were 1.3 (0.7), but the transfusional episode could not be related to prior chemotherapy.

With regard to the treatment administered for presurgical anaemia, it is notable that only 6 patients (1.3% of the total) received treatment with erythropoiesis stimulating agents (EPO), 40 (8.5%) were treated with iron, and 15 (3.2%), with vitamin B_{12} or folic acid. Of these, 74% had not received previous treatment with chemotherapy and/or radiotherapy.

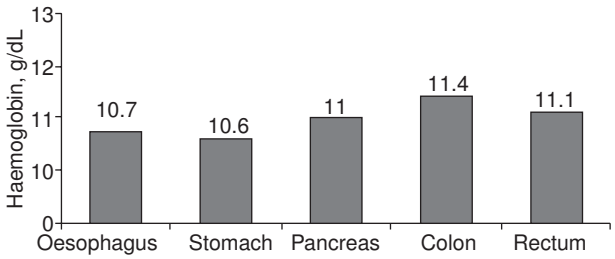

Figure 3 – Relationship between Karnofsky 30-80 and preoperative anaemia.

Table 2. Preoperative Values of Fe Metabolism and Inflammatory Profile

Parameter	No.	Value
Ferritin, ng/dL	80	217.3 (467)
Plasma Fe, µg/dL	87	60.3 (50)
Transferrin saturation rate (TSR), %	39	20.2 (12)
Total iron binding capacity (TIBC), mg/dL	22	299.8 (67)
Soluble transferrin receptor, nmol/L	5	2.8 (1)
C-reactive protein, mg/dL	34	6.4 (15)

Discussion

Numerous studies have described a high incidence of anaemia in patients with cancer. Dunne et al[8] investigated the incidence of preoperative anaemia in patients undergoing non-cardiac surgery, and found this in 34% of the 6301 patients studied. In our study, the mean presurgical Hb figure was 13.1 (2) g/dL.

When evaluating the presurgical Hb in terms of tumour location, there is a notably higher incidence of Hb <12.5 g/dL in digestive tract tumours, and it is concluded that 49% of patients with primary digestive tumours have a presurgical Hb <12 g/dL, and of them, 13% present figures of Hb <10 g/dL.

Preoperative anaemia in patients with cancer of the gastrointestinal tract is well documented.[9,10] Dunne et al[11] recently studied the incidence of preoperative anaemia in preoperative colorectal cancer and evaluated their risk factors. Of 311 patients, 46.1% had preoperative anaemia, more frequent in the right-hand locations and with a frequency that increases with age and according to the stage of the tumour.

The mechanism that causes the anaemia in the neoplasic patient is sometimes difficult to identify and is considered to be anaemia of the chronic disease. In its pathogenesis, part from the possible losses due to haemorrhage, other anomalies can contribute.[7] Preoperative anaemia has been associated with an increase in morbidity and mortality. In surgical patients, preoperative Hb values are related inversely to mortality.[12]

In the aforementioned study, Dunne et al[11] determined that preoperative anaemia is an independent risk factor for greater morbidity and mortality, and in the colorectal cancer it is a predictive factor for poor prognosis. Other studies, however, indicate that the anaemia associated with greater mortality is not anaemia per se, although transfusional practice increases the risk. In fact, anaemia is well

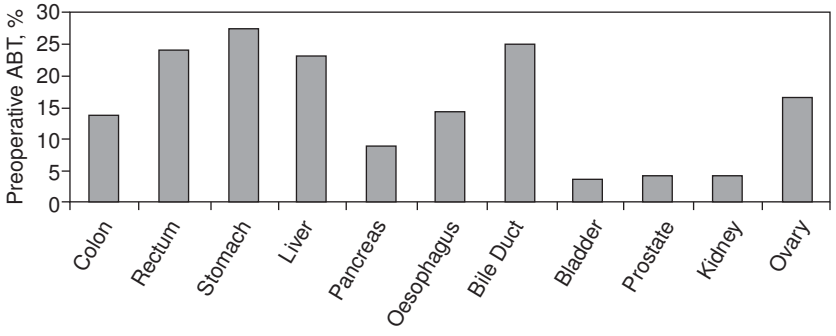

Figure 4 – Frequency of preoperative allogenic blood transfusion (ABT).

Table 3. Immunological Changes Associated to Allogenic Blood Transfusion

Descent in the T-cell ratio CD4/CD8
Decrease in the function of NK (natural killer) cells
Decrease in macrophage/monocyte function
Decrease in the function of T-suppressor lymphocytes
Changes in the activity of B lymphocytes
Reduction in the presentation of antigens
Increase in the production of PGE2
Alteration in the production of cytokines. Decreased production of interleukin 2

documented as a predictive factor of transfusional risk. Tartter et al[13] conducted a prospective study in 123 patients with colorectal cancer to identify the variables determining postoperative blood transfusion. The multivariate analysis shows several factors, including age, intraoperative blood loss and a low figure of haematocrit on admittance, such as significant transfusional risk factors.

Similarly, Benoist et al[14] determined that Hb ≤12.5 g/dL values are an independent risk factor for receiving blood transfusions in patients subject to surgical resection of rectal cancer.

There are data leading to the belief that the ABT is an independent risk in the development of postoperative infections, which increases tumour recurrence and decreases survival. However, the analysis of the results obtained in our study shows that only 12.9% of patients received some type of treatment for their anaemia during the preoperative period and that 15% received only preoperative transfusions to improve their haemoglobin levels.

The immune agents and mechanisms that are involved in immunodeficiency related to blood transfusion are still not entirely clear. Great variability in the alterations and changes induced by ABT in the tumoural and cellular response of the immune system have been reported[1,3,4,15] (Table 3). Different studies on these mechanisms propose a hypothesis that becomes stronger than the rest[3,16] and which are based on the stimulation of the response of the T *helper* cell 2 immunosuppression lymphocytes (Th) that annuls cell immunity and counteracts the "immunostimulators" produced by a response of the Th1.

There is currently no evidence available that provides irrefutable confirmation that ABT leads to an increase in the bacterial infections, increased tumour recurrence and decreased survival in oncological patients, because there may be other factors playing an important role.[3]

However, there are data from a large number of clinical studies that justify the need to make efforts to reduce the use of allogenic blood to the absolute minimum. Thus, Heiss et al,[17] in a study with 120 patients with colorectal cancer, found a significant difference in the rates of postoperative cancer when this was compared with patients receiving allogenic blood transfusions and those who received their own blood. Other studies came to the same conclusions, showing that blood transfusions are an independent risk factor in the development of postoperative wound infection,[18] postoperative infectious complications[19] and multiple organ failure.[20] In a study including 6301 patients undergoing non-cardiac surgery in 1995-2000, perioperative blood transfusion therapy was shown to be a predictive factor for infection and morbidity and mortality[8] and caused a greater demand of resources.

Postoperative bacterial infection was found in 39% of patients receiving transfusions, as opposed to 24% not receiving transfusions, meaning the risk of infection increases for patients receiving transfusions.[21] In a recent prospective study involving 740 patients undergoing elective surgery for colorectal cancer, an increase in postoperative infection in patients receiving RBC transfusion, although the leukocytes had been removed, with respect to those who did not receive transfusion therapy. In a multivariate analysis, the risk of death was also significantly higher in those who contracted infections.[22] The results of these and other studies have been the subject matter of a meta analysis in which the authors conclude that "there is no definitive evidence of the existence of an immunomodulatory effect of the ABT that causes an increase in relapse of cancer and/or postoperative bacterial infections," although this justified a high level of suspicion that the ABT associated immunomdulation really existed, and could increase the risk of postoperative infection by 10%.[4,23]

The relationship between ABT and a worse long term prognosis in oncological surgery is not clear, although the majority of studies in this respect show a correlation between tumour recurrence and ABT.[2] Heiss et al[25] conducted a randomised study on autologous blood and allogenic blood in colorectal surgery and found a greater tumour free survival rate in the autologous blood group. In the study of Bumblerg et al,[26] a revision of 197 patients treated for adenocarcinoma of the colon, a rate of recurrence of 9% was seen in patients who did not receive transfusions, as against a 43% rate of recurrence among the 129 patients requiring it. Two meta-analysis sought to summarise the data published to date regarding the relationship between ABT and surgery for colorectal cancer. In both cases, a significant increase in the risk regarding the prognosis was seen.[27,28] Among the alternatives that exist to reduce the transfusional risks, correcting preoperative anaemia appears to be a fundamental part of the strategy. Although there are several anomalies intervening in its pathogenesis, the administration of recombinant erythropoietin (EPO) stimulates erythropoiesis, promoting the proliferation of erythroid precursors and the maturation of the erythrocytes.

The perioperative administration of EPO and iron in anaemic patients with cancer undergoing surgery, decreases allogenic blood transfusions and/or the number of patients receiving transfusions and the frequency of postoperative complications.[29]

A prospective, double-blind, randomised study[6] showed that patients treated with EPO 300 U/kg/day for 14 days plus intravenous iron 100 mg/day improved significantly their values of preoperative and post operative Hb and decreased the risks of ABT by 51%. Similar results were found in other studies, although the translation of the increase in erythropoiesis in the reduction of the requirements for transfusion is variable depending on the dose of EPO administered and availability of vital substrates for: iron, vitamin B_{12} and folic acid.[30,31] In our study, only 6 (1.3%)

patients had received preoperative treatment with EPO, 40 (8.5%) had been treated with iron, and 15 (3.2% of the total) with vitamin B_{12} and folic acid. Of the patients treated pharmacologically for anaemia, 26% were given chemotherapy and/or radiotherapy.

Classical thought might draw the conclusion that the lack of preoperative treatment of these patients is due to the early indication for surgery after diagnosis; however, the analysis of the study data shows that in the majority of situation there is enough time available for optimal preoperative preparation of the patient (6.2 [6] weeks from diagnosis to the date of the surgery and 19.1 [23] days from the pre-anaesthetic visit).

We have therefore seen a deficient evaluation of the analytical parameters in the preoperative study. Nutritional deficit is known to have a general effect, not only on erythropoiesis, but on several aspects of the immune system.[32] No data is available in this study indicating whether using autologous blood would be a measure for saving allogenic blood in our oncological patients undergoing surgery. It would seem plausible that the autologous blood transfusion should present not only negative immunosuppressive effects, but that it would also have a beneficial stimulating effect.[6]

An adequate transfusional policy and save of blood can only be carried out in oncological surgery by first optimising the preoperative conditions of the patient. It is necessary to raise awareness that this preparation forms part of a surgical planning that seeks to avoid ABT and its possible complications. The study carried out shows that there is time available to establish preoperative protocols for the early diagnosis and treatment of anaemia.

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