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Original Paper

Increased Autologous Blood Donation in Rectal Cancer by Recombinant Human Erythropoietin (rhEPO)

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A randomised, placebo-controlled trial was conducted to study whether the subcutaneous administration of recombinant human erythropoietin (rhEPO) increases the donated red cell blood volume in patients with rectal cancer. Patients with resectable rectal cancer and a haemoglobin (Hb) level $\geq$ 12.5/ > 12 g/dl (males/females) were scheduled to receive pre-operatively either erythropoietin (200 U/kg body weight daily) ($n = 28$) or placebo ($n = 26$) subcutaneously for 11 days. During this period autologous blood was collected. No serious adverse events were attributed to erythropoietin. 20 of 28 patients treated with rhEPO were able to donate $\geq$3 units (71%) compared with 11 of 26 control patients (42%). The mean cumulative volume of red cells donated was 29% higher in the patients who received rhEPO (571 versus 444 ml, $P = 0.02$). The change in the mean reticulocyte value from baseline to the last pre-operative value was significantly higher in the rhEPO group (10.4 to 61.6‰ versus 11.0 to 20.1‰, $P = 0.0001$). The fall in the mean haematocrit from baseline to the last pre-operative value was significantly lower in the rhEPO group (41.4 to 37.6% versus 41.8 to 34.8%, $P = 0.0004$). rhEPO increases the ability of cancer patients to donate autologous blood during a short pre-operative period and enhances the restoration of haematological values after the donation period. © **1998 Elsevier Science Ltd. All rights reserved.**

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INTRODUCTION

HOMOLOGOUS BLOOD transfusions have contributed to the success of major surgery but there is increasing awareness of the disadvantages associated with blood transfusions. In addition to the general complications of homologous blood transfusions [1], retrospective and randomised studies [2–5] including the results of a meta-analysis [6] suggest that perioperative homologous blood transfusions may have an adverse effect on the prognosis in cancer surgery. But evidence for this is far from proven. Additionally, the rate of postoperative infectious complications may be increased if blood transfusions are given [4].

Alternatives to homologous blood transfusions such as preoperative deposit of autologous blood, pre-operative haemodilution, and reinfusion of blood saved during the operation have been developed. The pre-operative collection of autologous blood is limited by restrictions on the storage of red cells and by the patient's erythropoiesis. which may be related to an inadequate response to endogenous erythropoietin [7, 8]. Intra-operative cell saving in cancer surgery is problematic because of the possibility of introducing metastastic cells into the circulation.

Recombinant human erythropoietin (rhEPO) has been successfully used to increase the yield of autologous blood in patients undergoing orthopaedic or heart surgery [9–12]. In elective surgery there are no problems with regard to the time for pre-operative blood donation. Cancer patients, however, are confronted unexpectedly with their disease and surgery has to be performed shortly after diagnosis. Autologous blood donation is therefore usually limited as a result of the brief period between diagnosis and surgery.

In colorectal surgery, blood transfusions are needed in 65–86% of patients [13–15]. In these patients homologous

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transfusions could be avoided by pre-operative autologous blood donation. The feasibility of pre-operative blood donation in patients with colorectal cancer and a reduction in homologous blood transfusions has been demonstrated in several trials [3, 4].

In a randomised double-blind, placebo-controlled multicentre study we investigated whether epoetin beta (rhEPO) can increase pre-operative blood donation in patients with resectable rectal cancer.

PATIENTS AND METHODS

Eligibility criteria

Patients entering the study were required to have rectal cancer suitable for curative resection. All patients entering the study were advised of the goals and potential hazards of the treatment and gave their informed consent.

Patients were eligible for the autologous predeposit programme if they had a normal haemoglobin (Hb) level (males ≥ 12.5 g/dl; females > 12 g/dl) and a satisfactory physical status. Patients were ineligible if they had a history of cardiopulmonary insufficiency (uncontrolled hypertension, unstable coronary disease, unstable angina pectoris), obstructive or restrictive pulmonary disease, haematological disease, seizures, or active inflammatory, infectious or viral diseases that might compromise the response to rhEPO therapy. Patients who had received androgens, cytotoxic agents, immunosuppressive agents, or other agents known to affect erythropoiesis in the last 4 months before study entry were also excluded, as were pregnant women or those with unreliable contraception.

Criteria for stopping the study medication were diastolic blood pressure more than 100 mmHg despite antihypertensive therapy, seizures and unstable angina pectoris.

Study design

After giving written informed consent, patients were randomly assigned to receive rhEPO or placebo subcutaneously. The study protocol was approved by the Medical Ethics Committees of the Universities of Heidelberg and Berlin. The patients were administered the coded study medication starting 2 weeks before surgery. During the first 11 days (0–10) patients were to receive daily either 200 IU/kg body weight rhEPO (Recormon®, Boehringer Mannheim GmbH, Mannheim, Germany) or placebo (placebo lyophilisate). Patients were excluded from blood donation if they had a haemoglobin value less than 11.5 g/dl and/or a haematocrit lower than 34%. A unit of blood (400–500 ml) was scheduled to be collected from each patient twice a week for 2 weeks with a maximum of 4 units (at visits 2, 3, 4 and 5). The units were then stored until surgery. This donation period was chosen in accordance with current clinical practice in the treatment of rectal cancer patients. The last blood donation was 4 days before surgery. Each blood unit was separated and stored as red blood cell concentrate preserved in citrate-phosphate-dextrose-adenine (CAPD-1). Oral iron supplementation with ferrous glycine sulphate (200–300 mg Fe^{2+}) was given daily throughout the pre-operative phase. Observation phase I included the immediate post-treatment interval (approximately 2 weeks) and phase II the 12 weeks following surgery.

Tumour treatment

Surgery for rectal cancer followed standard oncological criteria with simultaneous resection of locoregional lymphatic nodes and mesorectal excision. Tumours 5 cm proximal to the anal verge were generally treated by abdomino-perineal resection (APR). Patients with tumours deeper within the rectum (up to 15 cm from the anal verge) underwent anterior resection (AR). Intra-operative blood loss was measured in the aspirator and blood on the surgery towels was also estimated. Blood transfusions were recommended for patients with Hb values less than 7.5 g/dl. The decision to give a blood transfusion was made by the attending anaesthesiologist or surgeon.

Postoperative adjuvant radio-chemotherapy was recommended for high-risk rectal cancer patients (pT3/pT4 tumours and lymph node metastasis) according to the U.S. National Institute of Health (NIH) consensus conference [16]. Radiotherapy consisted of fractionated administration of 50–60 Gy (5× 1.8–2 Gy/week) and continued with 5-fluorouracil/leucovorin chemotherapy.

Laboratory study

Laboratory tests were performed in all patients initially and at intervals during the study, and included complete blood count and reticulocyte count, electrolyte levels, assessment of liver and kidney function, prothrombin time, partial thromboplastin time, measurements of serum ferritin, transferrin and iron levels, and total iron binding capacity. The predicted red blood cell volume was calculated according to Nadler [17].

An enzyme-linked immunosorbent assay was used to detect antibodies to recombinant human erythropoietin in the serum [18].

Adverse events

Adverse events (AEs) were recorded throughout the entire study period. AEs were defined as any undesired or pathological changes in a patient as indicated by signs, symptoms, and/or laboratory changes that occurred in association with the use of a drug or placebo whether or not considered drug-related. An AE was classified as serious if it was life-threatening, if admission to hospital was necessary or if hospitalisation was prolonged. The causality of adverse events was assessed under blinded conditions.

Statistical analysis

All patients who entered the study and who were treated at least once with rhEPO beta or placebo were included in the analysis of efficacy based on intention-to-treat principles. The statistical null hypothesis was that the volume of autologous blood donated (cumulative red cell volume (RCV)) would be identical in both treatment groups. The cumulative red cell volume donated was calculated for each patient as follows.

$$\text{Cumulative RCV (ml)} = \frac{\text{Sum donated blood (ml)} \times \text{Hct of donated blood (\%)}}{100}$$

The hypothesis was tested using the exact Wilcoxon rank-sum test. In order to take into account the influence of the different baseline haematocrit levels and the associated variability of donation capacity on the donated RCV, the net cumulative RCV was calculated as a further variable for each patient.

$$\text{Net cumulative RCV (ml)} = \text{cumulative RCV (ml)} + \frac{\text{blood volume (ml)} \times (\text{final Hct} - \text{baseline Hct (\%)})}{100}$$

where baseline Hct = mean Hct at visits 1 and 2 and final Hct = last pre-operative Hct value.

The number of patients with homologous blood transfusions was analysed using Fisher's exact test. The clinical laboratory values from the baseline to the last available value of the pre-operative phase were analysed using Wilcoxon rank-sum tests. Only two-tailed statistical tests were performed. Statistical significance was indicated if the P value was below 0.05.

RESULTS

Patient characteristics

57 patients were enrolled in the trial. Of these, 54 were analysed for safety and efficacy. 3 patients in the placebo group withdrew their consent prior to treatment and blood donation without giving reasons. The clinical characteristics of the 28 patients in the erythropoietin group and the 26 patients in the placebo group are shown in Table 1. There were no relevant differences between the treatment groups with respect to age, sex and type of surgical procedure. Predicted blood volume and haematological variables at the start of the study (baseline) were similar.

4 patients (1 in the rhEPO group and 3 in the placebo group) did not complete the study, the rhEPO patient due to positive serology for hepatitis B, and the 3 placebo patients because of lack of compliance, blood donation impossible due to phlebotomy and administrative complications.

Blood donation

The analysis of the cumulative volume of red cells collected from the patients in each group is shown in Figure 1. The volume was determined by multiplying the volume of blood donated (in ml) by the haematocrit of the donated blood (as a percentage).

A significant difference in RCV between the rhEPO and placebo groups was found ($P = 0.02$). The mean RCV was 571 ± 184 ml in the rhEPO group and 444 ± 225 ml in the control group. Analysed by sex, the males and females in the rhEPO group donated a larger RCV (626 ± 185 ml and 473 ± 142 ml, respectively) than the patients in the placebo group (522 ± 224 and 298 ± 142 ml, respectively).

The net RCV gain per donor (gain of red cells under the assumption that haematocrit was identical at the beginning and at the end of donation phase) was significantly ($P < 0.0001$) higher in the rhEPO group than in patients who received placebo (Figure 2).

This resulted in donation of 83 units (mean 3.0 ± 0.8 units per patient) in the rhEPO group as compared with the 59 units (mean 2.3 ± 1.1 units per patient) of blood collected in the placebo group (Figure 3). During the 2-week period, only 1 patient (4%) in the rhEPO group compared with 8 patients (31%) in the placebo group could donate only a single unit of blood. 2 units were collected from 7 patients in each group. 3 autologous blood units were collected in 12 rhEPO patients (43%) versus 7 placebo patients (27%), while 4 units of blood were collected in 8 rhEPO patients (29%) and 4 placebo patients (15%).

Table 1. *Patient characteristics*

	rhEPO ($n = 28$)	Placebo ($n = 26$)
Age (yr)		
Mean (± SEM)	60.6 ± 7.5	62.1 ± 7.5
(range)	(43–77)	(43–75)
Sex		
Male	$n = 18$	$n = 17$
Female	$n = 10$	$n = 9$
Surgical procedure		
Anterior resection (AR)	$n = 19$	$n = 15$
Abdomino-perineal resection (APR)	$n = 9$	$n = 11$
Predicted blood volume (l)		
Mean (± SEM)	4.6 ± 0.8	4.7 ± 0.5
(range)	(3.2–6.5)	(3.6–5.7)
Baseline haematocrit (%)		
Male	42.1 ± 3.4	43.1 ± 2.9
Female	40.1 ± 3.2	39.5 ± 1.0
Baseline haematological variables		
Haemoglobin (g/dl)	13.8 ± 1.1	13.9 ± 1.1
Erythrocytes (10^{12}/l)	4.6 ± 0.5	4.6 ± 0.4
Reticulocytes (‰)	10.4 ± 5.3	10.7 ± 7.9
Corrected reticulocytes (‰)	9.6 ± 4.8	9.9 ± 7.1
Baseline values for iron metabolism		
Iron (μmol/l)	13.0 ± 4.9	14.5 ± 5.5
Ferritin (ng/ml)	157.9 ± 189.0	154.6 ± 163.7
Transferrin, saturated (%)	21.3 ± 8.5	23.9 ± 9.6
Transferrin (mg/dl)	285.1 ± 48.2	278.0 ± 47.0

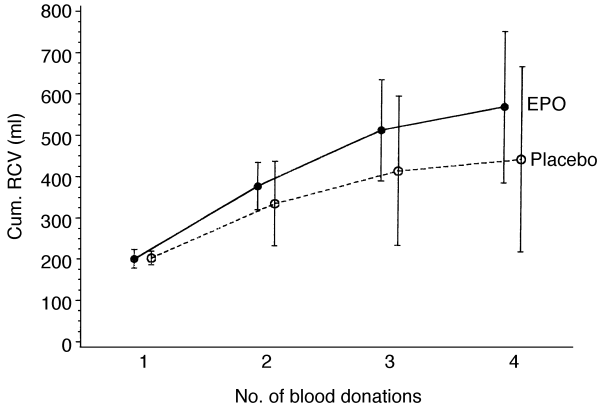

Figure 1. Correlation between cumulative red cell volume (cum. RCV) and the number of blood donations. Mean and standard deviation. w, week.

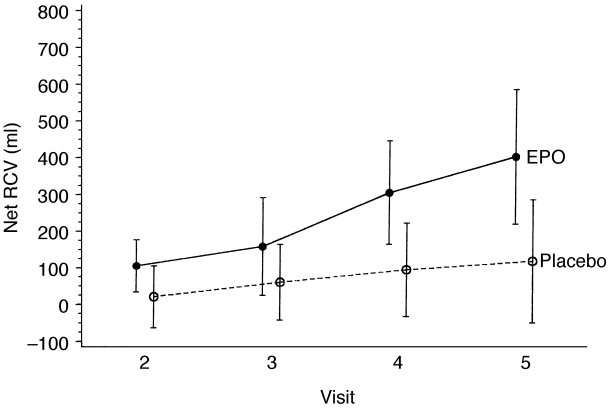

Figure 2. Course of mean (± S.D.) net RCV during the pre-operative treatment phase and interquartile ranges. Net RCV, Net to cumulative red cell volume (ml).

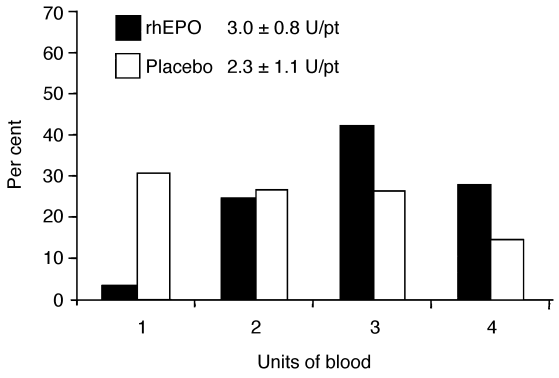

Figure 3. Units of blood donated by the patients.

Changes in haematological values

The course of reticulocytes is shown in Figure 4. A significant difference was found for the change from the mean baseline value (10.4 ± 5.4‰) to the last mean pre-operative value (61.6 ± 49.2‰) in the rhEPO group compared with the placebo group (11.0 ± 8.0‰ and 20.1 ± 21.5‰) ($P = 0.0001$). The course of the haematocrit during the study is shown in Figure 5 for patients in both groups. The fall in the mean value from baseline (41.4 ± 3.5%) to the last pre-operative value (37.6 ± 4.1%) was significantly lower in the rhEPO group than in the placebo group (41.8 ± 3.0% and 34.8 ± 2.8%) ($P = 0.0004$). On discharge the haematocrit in each study group was similar and after 12 weeks (visit 12) the haematocrit had returned to the levels at admission in both groups.

The initial Hb concentration (13.8 ± 1.2 g/dl) was almost achieved before surgery (12.1 ± 1.4 g/dl) in the rhEPO group, while a continual decrease was observed in the control group (from 13.9 ± 1.1 g/dl to 11.5 ± 1.1 g/dl).

All other haematological parameters (platelets, MCV median corpuscular haemoglobin (pg/cell); MCH median corpuscular volume (fl); and MCHC median corpuscular haemoglobin concentration (g/dl)) were not influenced by rhEPO as compared with placebo.

Changes in variables of iron metabolism

The fall in available iron (transferrin saturation) in the donation phase was similar in both groups ($P = 0.5$). The depletion of storage iron was significantly higher in the rhEPO group than in the placebo group ($P = 0.036$), as shown by the decrease in ferritin levels during the donation phase (data not shown).

Blood loss and transfusions

Analysis of intra-operative blood loss and the use of autologous blood transfusion is an interesting aspect, although this was not the principle aim of this trial. The cumulative blood loss per patient (intra-operatively and postoperatively during the first 48 h) was higher in the placebo group, but was not significantly different between the two groups ($P = 0.1$). In the rhEPO group patients lost 1411 ± 1093 ml of blood compared with 2064 ± 1574 ml in the placebo group. One patient with postoperative haemorrhage (total blood loss 6800 ml) received placebo. This patient received his one autologous blood unit and additionally 8 homologous blood transfusions.

During the peri-operative period 23 of 27 patients (85%) in the rhEPO group received autologous transfusions and 5 of 27 patients (19%) received homologous blood transfusions.

The figures for the placebo group were 19 of 23 patients (83%) and 9 of 23 patients (39%), respectively. However, this difference was not statistically significant ($P = 0.13$). 53 of the 83 autologous blood units (64%) donated in the rhEPO group were retransfused by patients undergoing surgery compared with 43 of 59 units (73%) in the placebo group. The 29/83 (35%) donated blood units were given intra-operatively to rhEPO patients versus 31/59 (53%) to placebo patients and postoperatively (up to 48 h after surgery) in 20/83 (24%) of rhEPO versus 10/59 (17%) of placebo patients. 4 units in the rhEPO group and 2 units in the control group were retransfused 48 h after surgery. Overall, 9 of 62 (15%) transfused units of blood were homologous in the rhEPO group compared with 33 of 76 (43%) in the placebo group.

Adverse events

Slightly more patients reported AEs in the rhEPO group (82%) than in the placebo group (69%). When analysing AEs, it is appropriate to separate the pre-operative period, in which the influence of the study treatment and blood donation predominate, from the postoperative period, in which the influence of surgery is dominant. The incidence of AEs (at least one) with onset in the pre- and postoperative periods was (57% and 74%, respectively) in the rhEPO group and (38% and 57%, respectively) in the placebo group (Table 2).

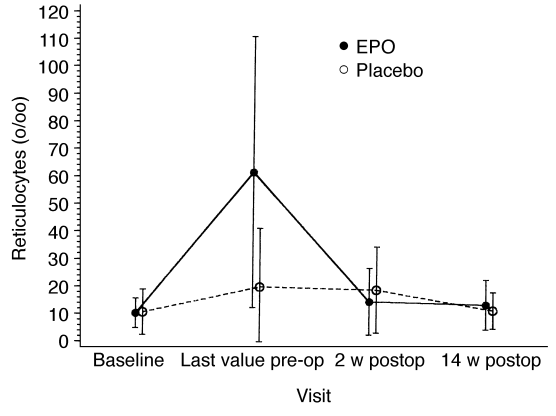

Figure 4. Reticulocytes: Mean (± S.D.) reticulocytes at baseline, last pre-operative value (last pre), course during postoperative phase and interquartile ranges. (Baseline, visits 1 and 2.)

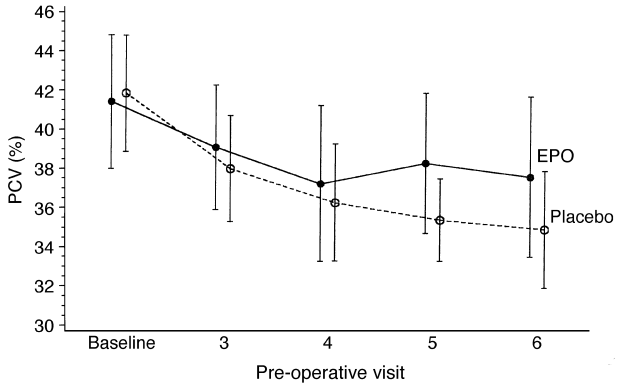

Figure 5. PCV: Course of the mean (± S.D.) during the preoperative treatment phase and interquartile ranges. (Baseline, visits 1 and 2.)

Table 2. All adverse events observed during the treatment period

Adverse event	rhEPO		Placebo	
	Pre-operative $n = 28$ (%)	Postoperative $n = 27$ (%)	Pre-operative $n = 26$ (%)	Postoperative $n = 23$ (%)
Body as a whole	6 (21)	9 (33)	3 (12)	9 (39)
Cardiovascular system	3 (11)	8 (30)	2 (8)	3 (13)
Respiratory system	2 (7)	1 (4)	1 (4)	3 (13)
Urogenital system	—	6 (22)	—	5 (22)
Digestive system	7 (25)	8 (30)	6 (23)	6 (26)
Blood and lymphatic system	1 (4)	1 (4)		3 (13)
Injection site reaction	2 (7)			
Metabolic and nutritional disorders	3 (11)	12 (44)		5 (22)
Musculoskeletal system				3 (13)
Nervous system	5 (18)	3 (11)	2 (8)	2 (9)
Special senses	3 (11)			1 (4)
Skin and appendages		2 (7)	1 (4)	2 (9)
At least one	16 (57)	20 (74)	10 (38)	13 (57)

In the pre-operative period there were somewhat higher incidences of dizziness (4 pts. 14% versus none), asthenia (2 pts. 7% versus none) and chills and fever (3 pts. 11% versus none) in the rhEPO group (Table 3). These AEs are closely related to blood donation and the higher frequency observed may be a result of the higher frequency of blood donation in the rhEPO group. Postoperatively, higher frequencies were found in the rhEPO group for healing disturbances (5 pts. 19% versus 3 pts. 13%) hypoglycaemia (2 pts. 7% versus none) and peripheral oedema (3 pts. 11% versus 1 pt. 4%).

Table 3. All pre-operative adverse events observed during the treatment period

Adverse events	rhEPO $n = 28$ (%)	Placebo $n = 26$ (%)
Body as a whole		
Asthenia	2 (7)	—
Pain	4 (14)	2 (8)
Chills, fever	3 (11)	—
Accident	—	1 (4)
Cardiovascular system		
Arrhythmia	2 (7)	—
Hypertension	2 (7)	1 (4)
Hypotension	1 (4)	1 (4)
Digestive system		
Constipation	2 (7)	4 (15)
Diarrhoea	4 (14)	2 (8)
Nausea	1 (4)	1 (4)
Blood and lymphatic system		
Thrombocythaemia	1 (4)	—
Injection site reaction		
Pain	2 (7)	—
Metabolic and nutritional disorders		
Hyperglycaemia	1 (4)	—
Hypokalaemia	3 (11)	—
Nervous system		
Dizziness	4 (14)	—
Sweating increased	2 (7)	2 (8)
Respiratory system		
Cough increased	2 (7)	1 (4)
Special senses		
Eye disorders	2 (7)	—
Otitis media	1 (4)	

None of these AEs was assessed as being possibly related to the study medication.

During the treatment phase no severe complications were observed with exception of 1 patient with otitis media. Postoperatively, serious AEs were reported in a total of 9 patients, 7 of whom had received rhEPO (Table 4).

Most of these serious adverse events observed in the rhEPO group in the postoperative period were directly related to postsurgical complications (sepsis, ventricular fibrillation, ileus, wound healing disturbances, anastomotic leakage). Due to a complication of the central venous catheter occlusion of the basilic vein occurred in 1 patient on the sixth postoperative day. 1 patient died of pulmonary embolism. This patient collapsed on the sixth postoperative day without prodromal symptoms. The haematological parameters did not indicate a causal involvement of rhEPO. All serious AEs were assessed as unrelated to the trial medication.

DISCUSSION

Homologous blood transfusion is linked with an immunosuppressive effect and may have a negative clinical impact on the result of curative resected malignant disease [3, 4, 19]. Furthermore, homologous transfusions are associated with postoperative infections [4, 20]. Postoperative wound healing disturbances have been observed to be dose-related to blood transfusions [21]. The influence of homologous transfusions on tumour recurrence and patient survival is still controversial [6, 22].

In contrast retransfusion of autologous blood has far less immunological effects than homologous blood [23, 24]. However, transfused autologous blood is still a transfusion with cells that have spent several days in plastic containers. resulting in damaged cells, activated cells and cytocins, which can influence immunosuppression in patients [25, 26]. Thus, evidence that allogenic blood transfusion influences clinical outcome means that in deciding on whether to transfuse one must consider both risks and benefits of a transfusion. However, the use of autologous blood could improve clinical results.

The ability to donate a sufficient volume of blood for cancer patients is often restricted by a low haematocrit and a poor general condition in many patients as a result of the primary disease. A low haematocrit is often due to rectal

Table 4. Serious adverse events observed during the treatment period

Adverse event	rhEPO		Placebo	
	Pre-operative	Postoperative	Pre-operative	Postoperative
Otitis media	1	–	–	–
Anastomotic leakage	–	1	–	1
Fistula	–	1	–	1
Pyelonephritis	–	1	–	–
Urinary retention	–	–	–	1
Thrombosis (basilic vein)	–	1	–	–
Ventricular fibrillation	–	1	–	–
Pulmonary embolism	–	1	–	–
Ileus	–	1	–	–

tumour bleeding and is frequently combined with low iron levels. The efficacy of rhEPO is due to an increased production of RCV as a result of increased erythropoiesis accelerating the conversion of stored iron into circulating iron [27]. Therefore iron supplementation is an essential adjunct to rhEPO treatment.

With iron substitution only, patients with colorectal cancer were able to donate 1.6 units of blood during a pre-operative 10-day period, significantly reducing homologous blood transfusion in 52% of patients [4, 28]. In our study, it was possible to collect up to 3.0 ± 0.8 units of blood per patient in the rhEPO group compared with 2.3 ± 1.1 units in the placebo group.

Pre-operative autologous blood donation programmes reduce homologous blood transfusions [4, 15]. Allogenic blood transfusion was reduced from 60% in the control group to 33% in the donation groups ($P = 0.009$) [4]. The need for blood transfusions is, in practice, mainly determined by the pre-operative Hb level, blood loss during surgery, and the Hb level that is acceptable during and after surgery [29]. The donated blood units were retransfused peri-operatively (up to 48 h after surgery) in 59 and 69% of rhEPO and placebo patients, respectively. This figure might reflect phlebotomy-induced anaemia as reported in other studies [4, 9, 15]. Another reason for autologous blood transfusion could be the more liberal use of autologous blood in patients who became hypovolemic during surgery [30]. In the present study, the haemoglobin concentration and the haematocrit nearly returned to baseline before surgery in the rhEPO group, while a continuous decrease was observed in the control group.

In our study 9 of 62 (15%) transfused units of blood were homologous in the rhEPO group compared with 33 of 76 units (43%) in the placebo group. Blood loss in the placebo group was not significantly higher than in rhEPO-treated patients. With respect to homologous transfusion, the small number of patients in the current study meant that it was not possible to demonstrate statistically significant differences between the two groups. However, it was not the aim of the study to analyse the amount of retransfusion. The efficacy and safety of erythropoietin has been evaluated in cancer patients in the treatment of anaemia associated with the disease or chemotherapy. There was no negative impact on tumour growth [4, 31]. In predeposit autologous donation programmes rhEPO has been demonstrated to be effective in increasing the volume of autologous blood. Significantly more patients treated with rhEPO (100% for 600 IU/kg; 97% for 300 IU/kg) were able to donate more than 4 units of blood compared with placebo (78%; $P < 0.05$) [32], but all these trials involved elective surgery [9, 11, 32–34]. However, wastage of up to 77% of collected blood as reported in other studies [9, 11, 35] is a disadvantage of this strategy and reduces cost-effectiveness. Furthermore, unnecessary phlebotomies are inconvenient for the patient and constitute an increased risk. In the present study, for the rhEPO group, 30/83 (36%) and for the placebo group, 16/59 (27%) autologous blood was wasted.

rhEPO has mainly been administered intravenously to autologous blood donors [10–12, 27, 36], but the subcutaneous route has been shown to be more effective [37]. Subcutaneous use also allows the possibility of self-injection. The present dose of 200 IU/kg body weight is comparable with the intravenous dose used previously [11, 36], but it was given over a shorter study period. However, our results showed that the pre-operative Hb value had nearly returned to baseline despite phlebotomy.

In this study the volume of red cells donated by patients treated with erythropoietin was 29% ($P = 0.02$) higher than in the placebo group. In randomised trials using erythropoietin to increase pre-operative blood donation, a 35–60% higher yield of red cells than in placebo-treated patients has been achieved [10, 11, 36]. In the current trial, 11 of 26 (42%) patients treated with placebo were able to donate ≥ 3 units of blood compared with 20 of 28 (71%) of patients given rhEPO. However, a longer donation period allows more blood to be donated without erythropoietin therapy. In elective surgery 71% of patients donated more than 4 units of blood without further medication in a 3-week pre-operative period [10].

The AEs observed in the pre-operative treatment phase were related to the blood donation itself or the underlying disease rather than to the trial medication. AEs observed after surgery were most probably explained by postsurgical complications.

One patient died of pulmonary embolism without prodromal symptoms on the sixth postoperative day. Haematological data showed no pathologically increased values. All serious AEs were assessed as being unrelated to the study medication.

Patients requiring surgery who are assessed as needing more than 2 units of blood may be one group in surgical oncology that will benefit from erythropoietin medication in a pre-operative donation programme, especially if the initial blood volume is below 4.0 1 and the Hb concentration below 12 g/dl [10, 11]. This study demonstrated the efficacy of subcutaneously administered recombinant human erythropoietin

in enhancing erythropoiesis and increasing the yield of autologous blood donated in a short pre-operative period in rectal cancer patients.

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