Avoidance of Allogeneic Blood Transfusions by Treatment With Epoetin Beta (Recombinant Human Erythropoietin) in Patients Undergoing Open-Heart Surgery

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In a double-blind, randomized, placebo-controlled trial, we evaluated the ability of epoetin beta (recombinant human erythropoietin) to avoid allogeneic blood transfusions (ABT) and the associated risks in patients undergoing primary elective open-heart surgery and in whom autologous blood donation (ABD) was contraindicated. Seventy-six patients overall were enrolled onto the trial and were randomly assigned to the two treatment groups, 5 × 500 U/kg body weight (BW) epoetin beta or placebo intravenously over 14 days preoperatively. All patients received 300 mg Fe^{2+} orally per day during the treatment period. Preoperatively, the mean hemoglobin increase was 1.50 g/dL greater in epoetin beta patients than in placebo patients (95% confidence interval, 1.10 to 1.90 g/dL), allowing a rapid return to the baseline value by the seventh postoperative day in most epoetin beta patients. The mean volume of blood collected by intraoperative isovolemic hemodilution was 562 mL (red blood cell mass, 274 mL) in the epoetin beta group and 218 mL (red blood cell mass, 94 mL) in the placebo group, respectively. Only four patients (11%) in the epoetin beta group received an ABT, compared with 19 (53%) in the placebo group (P = .0003). Epoetin beta was most useful in patients with a perioperative blood loss greater than 750 mL, in those with a baseline hematocrit value less than 0.42, and in those aged ≥60 years. The iron supplementation proved adequate despite the fact that a significant decrease in ferritin (median, 48.1%) and transferrin saturation (median, 40.5%) was observed in epoetin beta patients preoperatively. No influence of epoetin beta therapy on blood pressure, laboratory safety variables, or the frequency of specific adverse events was observed. Intravenous epoetin beta treatment of 5 × 500 U/kg BW in combination with 300 mg Fe^{2+} orally per day administered over 14 days preoperatively is an adequate therapy for increasing mean hemoglobin levels by approximately 1.50 g/dL and reducing the allogeneic blood requirement in patients undergoing elective open-heart surgery and in whom ABD is contraindicated.

ELECTIVE SURGERY is by far the most important reason for allogeneic blood transfusion (ABT). Ten percent of all annual red blood cell (RBC) transfusions are administered in coronary artery bypass surgery.[1] In the attempt to avoid ABT and the associated risks, and in view of the growing shortage of donated blood, great efforts have been made in recent years to develop blood-saving techniques and treatments.[1-3] As a result of improvements to existing strategies and the introduction of new ones, together with stricter indications for ABT, approximately 30% to 70 % of all cardiac operations are currently performed without ABT.[1,4] Since the hemoglobin (Hb) level is a key determining factor in perioperative ABT requirement, the use of recombinant human erythropoietin (rhEPO) to stimulate erythropoiesis and increase the Hb level in order to avoid ABT is one of the strategies currently being investigated in this area. This drug has been successfully used for many years in the treatment of renal anemia and has also been used in autologous blood donation (ABD) to increase the amount of available blood.[5-8]

The practice of multiple ABD preoperatively is occasionally not possible due to logistical problems (costly in terms of personnel and time, stressful to the patient, and lack of suitable facilities) or specific contraindications. Additionally, the number of patients with severe heart disease (aortic valve stenosis, poor left ventricular function, main left-stem stenosis, and New York Heart Association [NYHA] heart failure stage III to IV) undergoing cardiac surgery has generally increased due to recent improvements in intensive care medicine, the technique of extracorporeal circulation, and surgical techniques. These patients are contraindicated for ABD, because the restricted cardiac function means that the blood loss during ABD cannot be compensated for. Therefore, these patients are frequently dependent on ABT.[8,9]

The use of high-dose rhEPO treatment preoperatively without concomitant ABD is a new concept for avoiding ABT in open-heart surgery for those patients unable to donate autologous blood and for those with religious objections to ABD and ABT.[10,11] This placebo-controlled, double-blind trial investigated whether a significant saving in ABT could be achieved perioperatively by the preoperative administration of rhEPO (epoetin beta) in patients undergoing elective open-heart surgery in whom ABD was contraindicated.

PATIENTS AND METHODS

Ethical committee and patient eligibility, trial treatment, and follow-up evaluation. The trial protocol was approved by the Ethical Committee of Charité Hospital, Humboldt University Berlin. Patients aged 18 to 80 years undergoing elective open-heart surgery and with contraindications for ABD (Table 1) were enrolled into this trial after providing informed consent. The exclusion criteria

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Table 1. Number of Patients in the Analysis of Efficacy With Various Contraindications for Preoperative ABD in Both Groups

Contraindications	Epoetin Beta (n = 36)	Placebo (n = 36)
Aortic valve stenosis	12	6
LVEF < 40%	10	10
Left coronary main stem stenosis > 50%	7	1
Myocardial infarction < 6 months preoperatively	8	13
Heart failure stage NYHA III-IV	9	8
History of unstable angina pectoris	5	3
Exercise capacity < 70 W	7	5
Severe cardiac arrhythmias	5	4
History of TIA or syncope	2	0
Heart rate < 55/min	0	1
Pronounced lung disease	0	1

Fifteen epoetin beta and 21 placebo patients had 1 contraindication. Two contraindications were present in 14 patients in each group, 3 contraindications in 6 epoetin beta patients and 1 placebo patient. Four contraindications were observed in 1 epoetin beta patient.

Abbreviation: TIA, transient ischemic attack.

were diastolic blood pressure greater than 100 mm Hg, hematocrit (Hct) level greater than 0.45, convulsions or epilepsy, platelet count greater than 450×10^9/L, malignant tumor, acute infections, pregnancy, lactation, or inadequate contraception.

The trial medication was assigned to patients on the basis of the chronologic enrollment of patients and the sequential order of the blinded trial medication in a randomization list, determined by a random algorithm. The trial medication, 500 U epoetin beta or placebo/kg body weight (BW) intravenously, was administered on preoperative days 14, 10, 7, 5, and 2. The dosage was selected on the basis of a study in orthopedic patients that showed a mean Hct increase of approximately 0.06 within 14 days after a total dose of 2,500 U/kg BW administered as five single doses of 500 U/kg BW subcutaneously twice weekly compared with no treatment.[6]

The trial medication was not administered if any of the following events occurred: Hct greater than 0.50 or increase in Hct greater than 0.06 over baseline, platelet count greater than 500×10^9/L, adverse events rendering continuation of treatment unacceptable from a medical point of view, diastolic blood pressure greater than 110 mm Hg, and convulsion. All patients received daily oral doses of 300 mg Fe^{2+} (iron-glycine-sulfate) during the 14-day treatment period. Adverse events were documented continually. Blood pressure and blood picture were determined on the days of administration, immediately before operation and on the second, fifth, and seventh postoperative days. Ferritin, iron, transferrin and transferrin saturation, AST, ALT, creatinine, sodium, potassium, creatine kinase, leukocytes, and differential white cell count were determined at the start of treatment, immediately before operation, and on the seventh postoperative day.

Outcome event, blinding and transfusion policy, and operation type. The primary outcome was the percentage of patients with allogeneic intraoperative or postoperative blood transfusion. Secondary outcomes included the mean number of perioperative allogeneic blood units per patient (1 U = 300 mL packed RBCs), hematologic parameters, and parameters of iron metabolism. To evaluate safety, blood pressure, adverse events, and various laboratory parameters were compared in the two groups.

The trial was performed under double-blind conditions. Neither the transfusing anesthetists nor the surgeons were aware of the hematologic values measured at baseline and the changes during the treatment phase required to maintain blinding. For the purposes of surgical preparation, they merely received the actual hematologic results measured 2 days before surgery, with the exception of reticulocyte count. The decision to give intraoperative and postoperative transfusions was based on Hb/Hct levels and clinical need in accordance with the severity of heart disease in our patients. The decision thus accorded with modern transfusion guidelines for these patients.[2,12,13] During cardiopulmonary bypass (CPB), a Hb level less than 6.9 g/dL or a Hct level less than 0.21, and postoperatively a Hb level less than 8.5 g/dL or a Hct level less than 0.26, were used as intervention thresholds. All patients falling below these transfusion thresholds were transfused.

Patients in our trial exclusively underwent primary elective open-heart surgery. Coronary artery bypass grafting (CABG) as the sole procedure was roughly evenly distributed across both groups (placebo, n = 23; epoetin beta, n = 22). Ventricular aneurysm resection (VAR) as the sole procedure was performed in two epoetin beta patients. VAR with CABG was undertaken in one patient in each group. Aortic valve replacement (placebo, n = 8; epoetin beta, n = 12) was undertaken as the sole procedure in all cases, except for one placebo patient who also underwent CABG. Mitral valve replacement was only performed in the placebo group (n = 4; in one patient combined with CABG). In all patients, normothermic CPB was performed. The aprotinin medication in all patients consisted of an initial intravenous bolus of 2.0 million units infused over 25 minutes and of 2.0 million units in the priming volume of the heart-lung machine. RBC saver systems were only used postoperatively in two placebo patients. Whenever possible, intraoperative blood was collected before CPB by isovolemic hemodilution. Intraoperative hemodilution was performed subject to the following conditions: no acute myocardial infarction in the immediate preoperative period, no hemodynamic instability or sign of ischemia during the anesthetic induction, and Hct value of $\geq$0.39 preoperatively. The volume of blood (maximum, 10 mL/kg BW) withdrawn was calculated from the estimated blood volume of the patient, the priming volume, the cardioplegia volume, and the Hct level immediately before surgery so as to yield a Hct not less than 0.25 immediately after the start of CPB. Blood was removed from the central venous line and simultaneously replaced with an equal volume of crystalloid solution.

Calculation of sample size and statistical analyses. A retrospective review of 70 consecutive patients contraindicated for preoperative ABD suggested that approximately 70% of placebo patients would require ABT. Based on these data, the sample size calculation showed that a total of 2×36 assessable patients would be needed to detect a reduction from 70% to 35% during epoetin beta treatment, with a power of 0.8 and 2-sided significance levels of .05.[14]

All patients undergoing cardiac surgery with an assessable primary outcome were included in the analysis of efficacy of our trial. The rates of transfused patients in each treatment group (primary outcome) were compared by Fisher's exact test. The odds ratio for needing ABT during epoetin beta treatment versus placebo was calculated. The numbers of units transfused per patient were analyzed by the exact Wilcoxon rank-sum test. Continuous laboratory variables at various visits were compared by analysis of covariance with the baseline value as a covariate. Estimates of the differences between the treatment groups and corresponding 95% confidence intervals (CIs) were reported for the primary outcome and the laboratory variables of the secondary outcome. The influence of ferritin and transferrin saturation at baseline on preoperative Hb change in epoetin beta patients was investigated by regression analysis. Multiple logistic regression analyses (maximum likelihood method, stepwise selection technique) were performed to examine the risk factors for ABT and to calculate the odds ratio for needing ABT during epoetin beta adjusted for significant covariates. Significant covariates were

Table 2. Demographic, Clinical, and Laboratory Characteristics of Patients Undergoing Elective Open-Heart Surgery Given 5 × 500 U/kg BW Epoetin Beta Placebo Intravenously Within 14 Days Preoperatively

	Mean ± SD in Trial Group		
	Epoetin Beta (n = 36)	Placebo (n = 36)	Difference Between Means (95% CI)
Male/female (n)	28/8	28/8	—
Age (yr)	54.3 ± 8.6	57.0 ± 8.8	−2.7 (−6.8-1.4)
BW (kg)	79.1 ± 14.1	75.4 ± 11.7	3.7 (−2.4-9.8)
Height (cm)	171.9 ± 8.8	170.3 ± 7.3	1.6 (−2.2-5.5)
Blood volume (mL)*	4945.7 ± 822.5	4762.5 ± 699.4	183 (−178-544)
LVEF (%)	53.9 ± 17.2	50.9 ± 14.5	3.0 (−4.8-10.9)
Ischemia time (min)	46.6 ± 17.9	46.6 ± 16.0	0.0 (−8.0-8.1)
CPB time (min)	78.4 ± 22.3	79.4 ± 18.6	−1.0 (11.1-9.1)
Total blood loss (mL)	855 (595-1030)†	695 (565-1050)†	70 (−70-230)‡
Physical status (%)§			
ASA II	5.5	11.1	—
ASA III	94.5	88.9	—

* Calculated according to Nadler et al.[15]

† Median (interquartile range).

‡ Hodges-Lehmann estimate.[33]

§ American Society of Anesthesiologists Classification System.

categorized so as to illustrate the effect of epoetin beta on transfusion need in the resulting subgroups. Two-tailed tests were used exclusively. A *P* value less than .05 was considered to indicate statistical significance.

RESULTS

Patient characteristics and therapy. Thirty-eight patients were randomly allocated to each group and received trial medication. Three patients (placebo: one because of myocardial infarction, one because of indication for surgery no longer present; and epoetin beta: one because of acute left heart failure) were withdrawn during the treatment phase before the planned operation. Transfusion requirements could not be determined for one epoetin beta patient (death on first postoperative day, no blood transfusion). Thus, 36 patients per group were included in the analysis of efficacy.

No significant differences were apparent between the groups for the following parameters: sex ratio, baseline values of all laboratory parameters, BW, height, age, predicted blood volume,[15] left ventricular ejection fraction (LVEF), CPB time, ischemia time, and total blood loss (Table 2). No differences were apparent between the two groups in respect of time under anesthesia or length of hospitalization. All patients took the scheduled iron medication (as evaluated by questioning and checking of the iron medication package), which was well tolerated. No adverse events that could have been attributed to the preoperative iron medication (eg, obstipation or gastroenteric impairments) were reported in any patient.

Hematologic and iron parameters. The increase in Hb levels between baseline measurements and those before surgery was 1.50 g/dL greater in the epoetin beta group (95% CI, 1.10 to 1.90 g/dL) than in the placebo group (Table 3). The postoperative Hct nadir was 0.060 lower in placebo patients than in epoetin beta patients (95% CI, 0.042 to 0.078). The baseline Hct was achieved by the seventh postoperative day in 55.6% of patients treated with epoetin beta, compared with just 8.3% of placebo patients at the same point. Preoperatively, iron, ferritin, and transferrin saturation decreased by 41.7%, 48.1%, and 40.5%, respectively (median change), in the epoetin beta group, but increased in the placebo group (Table 3). Postoperatively, transferrin saturation and iron fell and ferritin increased in both groups. The iron parameters were almost identical in both groups at the end of the trial. The preoperative increase in Hb in the epoetin beta group was independent of ferritin and transferrin saturation at baseline.

Blood transfusions. As a result of the Hb/Hct increases, it was possible to perform intraoperative isovolemic hemodilution before CPB in 34 epoetin beta patients, compared with just 17 placebo patients. The mean volume of collected blood was 562 mL in the epoetin beta group and 218 mL in the placebo group ($P < .001$). On the basis of the immediate preoperative Hct value, this corresponds to RBC masses of 274 mL (epoetin beta) and 94 mL (placebo). Nevertheless, the Hct level during CPB in epoetin beta patients was slightly higher than in placebo patients. The total volume of blood collected by hemodilution was retransfused at the end of CPB and after the administration of protamine.

In total, 19 placebo patients (52.8%) and four epoetin beta patients (11.1%) received perioperative ABT (odds ratio, 0.112; 95% CI, 0.033 to 0.382; $P = .0003$). The total mean transfusion requirement per patient was considerably higher in the placebo group (1.67 U) than in the epoetin beta group (0.44 U; $P = .0002$). Only 5.6% of epoetin beta patients received ≥2 U of allogeneic blood, compared with 41.7% of placebo patients.

Intraoperatively, four placebo patients (11.1%) and one epoetin beta patient (2.7%) received ABT. Only one patient (placebo) was below the transfusion threshold (Hb <6.9 g/dL or Hct <0.21). The other four patients were above this threshold at the end of CPB, but were either suffering from

Table 3. Hematologic Variables and Parameters of Iron Metabolism in Both Groups 14 Days Preoperatively, Immediately Before Surgery, and 7 Days Postoperatively

Variable	Treatment Group	14 Days Preoperatively	Day of Surgery Preoperatively	7 Days Postoperatively
Hb (g/dL)	Epoetin beta (n = 36)	14.31 ± 0.98	15.84 ± 1.11*	13.41 ± 2.11†
	Placebo (n = 36)	13.78 ± 1.03	13.97 ± 1.06	11.99 ± 1.80
	Difference (95% CI)‡		1.50 (1.10-1.90)	1.01 (0.21-1.80)
Hct (L/L)	Epoetin beta (n = 36)	0.42 ± 0.03	0.48 ± 0.03*	0.41 ± 0.06§
	Placebo (n = 36)	0.41 ± 0.03	0.41 ± 0.03	0.36 ± 0.04
	Difference (95% CI)‡		0.06 (0.05-0.07)	0.04 (0.02-0.07)
Reticulocytes (%)	Epoetin beta (n = 36)	1.30 ± 0.40	4.90 ± 1.49*	2.09 ± 1.21
	Placebo (n = 36)	1.33 ± 0.37	1.51 ± 0.52	2.42 ± 0.98
	Difference (95% CI)‡		3.41 (2.89-3.92)	−3.2 (−8.4-1.9)
Ferritin (ng/mL)	Epoetin beta (n = 36)	145 ± 126	78 ± 70*	319 ± 267 (n = 32)
	Placebo (n = 36)	118 ± 77	148 ± 83	309 ± 252 (n = 33)
	Difference (95% CI)‡		−86 (−106-−68)	−8 (−132-115)
Iron (μmol/L)	Epoetin beta (n = 36)	13.4 ± 5.3	8.2 ± 6.3*	7.0 ± 5.0 (n = 35)
	Placebo (n = 36)	12.8 ± 5.9	17.5 ± 5.7	7.0 ± 3.8 (n = 33)
	Difference (95% CI)‡		−9.6 (−12.2-−7.0)	−0.2 (−2.3-1.9)
Transferrin saturation (%)	Epoetin beta (n = 36)	19.3 ± 7.8	12.7 ± 8.3*	13.4 ± 13.1 (n = 35)
	Placebo (n = 36)	18.5 ± 8.9	28.4 ± 10.0	12.8 ± 10.4 (n = 31)
	Difference (95% CI)‡		−16.0 (−20.1-−12.0)	0.3 (−5.5-6.0)

* $P < .001$, comparison between both groups.
† $P < .05$, comparison between both groups.
‡ Baseline-adjusted difference (estimated by covariance analysis).
§ $P < .01$, comparison between both groups.

hypotension with tachyarrhythmia or showed signs of myocardial ischemia. The mean ABT requirement per patient was 0.17 U (placebo) versus 0.03 U (epoetin beta) intraoperatively.

Postoperatively, 17 placebo (47.2%) and three epoetin beta patients (8.3%) were transfused. The mean transfusion requirement per patient was 1.50 U (placebo) versus 0.41 U (epoetin beta) postoperatively. One placebo patient (severe lactic acidosis) and two epoetin beta patients (one with ventricular fibrillation and one with severe heart failure) were transfused even though they remained above the transfusion threshold (Hb <8.5 g/dL or Hct <0.26).

Possible factors influencing the ABT requirement were subjected to logistic regression analysis to describe subpopulations of patients who received the greatest benefit from the epoetin beta treatment and to adjust the results for the slightly unbalanced factors (age, baseline Hct, and blood loss). Multiple logistic regression analysis showed that the continuous covariates blood loss ($P = .0025$), age ($P = .0113$), and baseline Hct ($P = .0164$) were independent predictors for ABT requirement in addition to the epoetin beta effect ($P = .0013$). Significant interactions between these covariates were not found. Sex, BW, height, LVEF, baseline ferritin, baseline transferrin saturation, CPB time, ischemia time, and type of surgery were nonpredictive. The comparison of the unadjusted odds ratio for transfusion (0.112; 95% CI, 0.033 to 0.382) with the covariate-adjusted value (0.041; 95% CI, 0.006 to 0.288) indicates that the slightly unbalanced factors of blood loss, age, and baseline Hct level tended to produce an unfavorable effect, overall, for the epoetin beta group.

Epoetin beta treatment produced the most pronounced effect in those patient groups in whom the risk for ABT was highest, ie, in patients with blood loss greater than 750 mL or in patients aged ≥60 years or with a baseline Hct value less than 0.42 (Table 4). However, in subgroups with a low risk for ABT, epoetin beta treatment also led to a marked reduction in ABT. Multiple logistic regression analysis performed with the current data available on the day of surgery (without the inclusion of treatment group and blood loss as

Table 4. Allogeneic Blood Requirement Perioperatively in Epoetin Beta and Placebo Patients Stratified by Total Blood Loss, Age, and Baseline Hct Level

Explanatory Variable	Treatment Group	No. of Patients Included	No. (%) of Transfused Patients	Odds Ratio (95% CI)*
Total blood loss				
>750 mL	Placebo	17	14 (82.2)	0.05
	Epoetin beta	21	4 (19.1)	(0.01-0.32)
≤750 mL	Placebo	19	5 (26.3)	0.0
	Epoetin beta	15	0 (0.0)	(0.00-0.92)
Age				
≥60 yr	Placebo	18	14 (77.8)	0.03
	Epoetin beta	11	1 (9.1)	(0.00-0.35)
<60 yr	Placebo	18	5 (27.8)	0.35
	Epoetin beta	25	3 (12.0)	(0.05-2.23)
Hct at baseline				
≥0.42	Placebo	17	5 (29.4)	0.21
	Epoetin beta	25	2 (8.0)	(0.02-1.57)
<0.42	Placebo	19	14 (73.7)	0.08
	Epoetin beta	11	2 (18.2)	(0.01-0.62)

* An odds ratio <1 indicates a reduced risk for blood transfusions in patients treated with epoetin beta compared with placebo.

factors) suggests that preoperative Hct ($P = .0004$) and age ($P = .0185$) are independent predictors for the need for ABT in this model. The ABT rate in patients with a preoperative Hct ≤ 0.45 was 52.6%, compared with 8.8% in patients with a Hct greater than 0.45.

Safety. All patients who received the trial medications at least once (n = 76) were analyzed for safety. Adverse events most commonly observed were those involving the cardiovascular system (14 patients in each group) and metabolic and electrolyte imbalances (epoetin beta, n = 4; placebo, n = 9). Fever and/or infection postoperatively were recorded in four placebo patients and one epoetin beta patient. One fatality occurred in each group preoperatively (epoetin beta: acute left heart failure; placebo: myocardial infarction) and a further three fatalities per group postoperatively (epoetin beta: myocardial infarction, ventricular fibrillation, and cardiac tamponade; placebo: ventricular fibrillation, two septic shock). In addition to the eight fatalities, serious adverse events were observed in a further two epoetin beta and five placebo patients (epoetin beta: osteomyelitis and arterial bleeding; placebo: myocardial infarction, ventricular fibrillation, hypocoagulation, arterial bleeding, and osteomyelitis). These events only occurred in the postoperative phase and were considered to be normal complications of open-heart surgery. No negative effects of epoetin beta were apparent on the basis of the following laboratory safety variables: sodium, potassium, creatinine, AST, ALT, creatine kinase, leukocyte count, or differential white blood picture. A preoperative increase in blood pressure was observed in one epoetin beta patient with preexisting hypertension and was brought under control by increasing the antihypertensive therapy. Apart from this case, no notable differences in the course of blood pressure were discernible between the treatment groups. Thrombocytosis was not observed in either group during the treatment phase.

DISCUSSION

Treatment with 5 × 500 U epoetin beta/kg BW intravenously over 14 days preoperatively produced a significant increase in Hb level and improved the chances of being able to perform intraoperative isovolemic hemodilution before CPB in patients undergoing elective open-heart surgery. The epoetin beta therapy led to a significant reduction in allogeneic blood requirement, a marked increase in erythropoietic activity, a depletion of iron stores, and a rapid return to baseline levels of postoperative Hct values in most patients. Because of the higher preoperative Hct after epoetin beta therapy, the possibility of implementing intraoperative hemodilution (collected blood volume 2.6-fold higher than in the placebo group) and its effectiveness (collected RBC mass 2.9-fold higher than in the placebo group) are improved in the epoetin beta group.

The patients in our trial were contraindicated for ABD due to the severity of their underlying cardiac illness, an excessively narrow range of cardiac compensation, or diminished oxygen supply to the tissues. Accordingly, their risk of suffering postoperative complications was high.[16,17] In accordance with the severity of the heart disease, the transfusion threshold for Hct/Hb level should be higher in these patients than in patients with normal left ventricular function or without left ventricular hypertrophy in order to prevent serious complications.[12,13,18,19] It should also be borne in mind that Lewis et al found a strong correlation between Hb level less than 8.0 g/dL (at the first postoperative day) and an increase in early death in Jehovah's Witnesses undergoing cardiac surgery.[20] For patients without the mentioned risk factors, a wide range of transfusion thresholds (based on symptoms and vital signs) can be found in the literature (Hb 6.0 to 10.0 g/dL and Hct 0.18 to 0.30).[2,12,13] In view of the higher risk of postoperative complications in our patients, the transfusion thresholds used may be regarded as relatively low.

Age has been cited as a predictive factor for ABT in earlier studies and is often due to increased morbidity.[2,3] Additionally, in some elderly patients, the cardiac output does not increase in response to anemia.[2,19] The fact that age was found to be a predictive factor for transfusion need in our trial is due to the fact that only patients ≥ 60 years were transfused intraoperatively and that 12 of 18 placebo patients ≥ 60 years had a postoperative Hct nadir less than 0.26, compared with only five of 18 younger placebo patients. The baseline Hct value did not differ between these groups.

Some trials have been published on the use of rhEPO in a perioperative setting in patients not undergoing ABD. Below, and in Table 5, the results of our trial are compared with those obtained by The Canadian Orthopedic Perioperative Erythropoietin Study Group, Laupacis et al,[21] Kyo et al,[22,23] and by Biesma et al.[6] However, in the latter trial, the patients were treated with epoetin beta before elective hip replacement to correct the decrease in Hb levels after two ABDs. The transfusion threshold values in our trial were slightly lower (Hb <8.5 g/dL or Hct <0.26) than those employed by Laupacis et al (Hb <9.0 g/dL) and Biesma et al (Hct <0.30). These values are not specified in the trial by Kyo et al. The baseline values for Hb in the treatment groups and placebo/control groups were similar in all trials (Table 5). Compared with the blood losses in our trial, those observed by Laupacis et al were slightly lower and those observed by Biesma et al and Kyo et al slightly higher (Table 5). Multiple logistic regression analysis also identified a high Hb concentration or Hct value (baseline and preoperative values) and reduced blood loss as important predictive factors for reduced transfusion requirement in the three studies (Laupacis et al, Biesma et al, and our trial).

The reduction in ABT in our trial (11% *v* 53%) was greater than that observed in the trials by Kyo et al (50% *v* 58%) and Laupacis et al (23% *v* 44%). Kyo et al were unable to demonstrate any significant saving in ABT by preoperative rhEPO treatment alone. This was probably due to only a small preoperative increase in Hb resulting from the low preoperative dose of rhEPO ($\approx$700 to 1,000 U/kg within 14 days) and a blood loss roughly twice as high per kilogram BW as that in our trial. The blood loss per kilogram BW was estimated from the mean BW and the mean blood loss.[22]

The main reason for the more marked transfusion-reducing effect of our treatment regimen is probably the degree

Table 5. Comparison Between Our Trial Results and Those of Other Studies in Patients With Preoperative rhEPO Therapy Without Autologous Blood Donation and With the Study Results of Biesma et al[6]

Trial (indication) Preoperative Treatment With rhEPO/ Placebo and Iron	Trial Group	Mean ± SD				Rate of ABT (%)
		Baseline Hb (g/dL)	Hb Change From Baseline (g/dL)	Age (yr)	Total Blood Loss (mL)	
Our trial (cardiac surgery) 5 × 500 U rhEPO/kg (total, 2,500 U/kg) over 14 days IV; 300 mg Fe^{2+}/d orally over 14 d	rhEPO (n = 36)	14.31 ± 0.98	1.53 ± 0.82	54.3 ± 8.6	939 ± 493	11.1
	Placebo (n = 36)	13.78 ± 1.03	0.19 ± 0.92	57.0 ± 8.8	894 ± 557	52.8
Laupacis (orthopedic) 10 × 300 U rhEPO/kg (total, 3,000 U/kg) over 10 days SC; 3 × 300 mg iron-sulfate/d orally over 19 d	rhEPO (n = 77)	13.7 ± 1.2	0.88 (—)	64.0 ± 12	674 ± 446*	23
	Placebo (n = 78)	13.8 ± 1.2	−0.26 (—)	63.0 ± 12	725 ± 371*	44
Kyo (cardiac surgery) 4 or 6 × 9,000 U rhEPO (total, 700-1,000 U/kg) over 14 days IV; 6 × 40 mg Fe IV over 14 d	rhEPO (n = 18)	13.25 ± 1.90	0.8 (0.3)†	51.3 ± 14.5	1,250 (−)‡	50.0
	Control (n = 26)	13.80 ± 2.00	−0.5 (0.2)†	51.2 ± 13.9	1,350 (−)‡	57.7
Biesma (orthopedic) 6 × 500 rhEPO U/kg (total, 3,000 U/kg) over 21 days SC; 3 × 66 mg Fe^{2+}/d orally over 21 d§	rhEPO (n = 50)	14.05 ± 1.00	−0.27 ± 1.24	66.2 ± 8.0	1,225 ± 748	10.0¶
	Control (n = 45)	13.82 ± 1.19	−1.77 ± 0.69	65.9 ± 10.4	1,194 ± 608	35.6¶

Abbreviations: IV, intravenous; SC, subcutaneous; (—), SD not available.

* Only intraoperative blood loss specified in the report.

† Kyo et al.[23]

‡ Estimated by figure.[22]

§ Autologous blood donation 21 and 17 days preoperatively; data not included in publication[6]; D.H. Biesma and W. Franke, personal communciation, October 1993.

¶ Additionally, autologous blood was administered in 88.9% of controls and 46.0% of rhEPO patients.

of the preoperative increase in Hb. The Hb increase of 1.50 g/dL achieved by the epoetin beta therapy was higher, with a lower overall dose, than that recorded by Laupacis et al, even though subcutaneous administration of erythropoietin has been found to be more effective than the intravenous route in patients with renal anemia.[24,25] However, it is not known whether the findings for renal anemia with the more effective subcutaneous administration also apply to high-dose rhEPO therapy in patients with coronary artery disease. In these patients, the microcirculation, and thus the absorption of subcutaneously administered rhEPO, is likely to be impaired as a result of generalized arteriosclerosis. To prevent these factors from influencing the results on efficacy in the first study, we decided to opt for intravenous administration.

Evidently, the 10-day treatment period used by Laupacis et al, which is 4 days shorter than that used in our study, is not offset by the daily administration and the higher overall dose. This hypothesis accords with the investigations by Rutherford et al,[26] who showed that a reduction in the frequency of administration with the same overall dose (4 × 300 U/kg *v* 2 × 600 U/kg over a 10-day period) does not lead to a loss of efficacy. This trial also supports our assumption that prolonging the treatment period with the same overall dose leads to a greater increase in Hb values.

The saving in ABT reported by Biesma et al was achieved due to compensation of the Hb reduction resulting from ABD. However, the ABT rate was not lower than that in our own trial (10% *v* 11%), although a slightly higher total dose (20%) was used and two autologous blood units were available. Although both Kyo et al and Laupacis et al continued administration of rhEPO in the postoperative phase (14 and 3 days, respectively), the postoperative course of Hb was no more favorable than that observed in our trial, either compared with baseline or compared with the control group. We therefore conclude that postoperative administration of rhEPO is of little effect and is not indicated, especially in view of cost/benefit considerations.

The earlier postoperative normalization of Hct in the epoetin beta patients appears primarily to be influenced by erythroid precursor cells formed by epoetin beta therapy shortly before the operation. This was also observed in Jehovah's Witnesses treated with 4 × 500 U rhEPO/kg BW intravenously within 10 days preoperatively.[11] The increased formation of endogenous EPO triggered by low Hct during CPB is probably sufficient to cause maturation of preformed erythroblasts and rapid release of mature and immature reticulocytes from the bone marrow into the peripheral blood in the epoetin beta group. On the other hand, stress factors released in response to surgical tissue damage may inhibit early stages of erythropoiesis, thus leading to a reduction in the efficacy of postoperative rhEPO.[27,28]

Despite the oral iron therapy, plasma levels of iron and ferritin both decreased as a result of highly stimulated erythropoiesis with incorporation of iron during Hb synthesis. Authors of previous studies have suggested that erythropoie-

sis during rhEPO therapy with oral iron supplementation only responds effectively if transferrin saturation is greater than 20% or ferritin is greater than 100 ng/mL.[29,30] This hypothesis is not borne out by our trial. We found no correlations between ferritin and transferrin saturation at baseline and the preoperative course of Hb in the epoetin beta group. Furthermore, in the epoetin beta group, there was no difference with respect to the Hb increase (mean ± SD) in patients with transferrin saturation ≥20% (n = 14; 1.45 ± 0.63 g/dL) compared with patients with transferrin saturation less than 20% at baseline (n = 22; 1.58 ± 0.93 g/dL) and also in patients with ferritin ≥100 ng/mL (n = 20; 1.63 ± 0.64 g/dL) compared with patients with ferritin less than 100 ng/mL at baseline (n = 15; 1.58 ± 0.72 g/dL). Our results suggest that the daily oral administration of 300 mg Fe^{2+} provides sufficient iron therapy for the mean Hb increase of approximately 1.50 g/dL over a period of 14 days. The acceleration of erythropoiesis is known to be associated with an increase in intestinal iron absorption.[31] The intravenous iron administration as an alternative strategy proposed by other investigators was not required for effective erythropoiesis in our regimen. Similarly, Price et al have assumed that oral iron therapy during ABD with concomitant rhEPO therapy is sufficient since the RBC production rate were modestly reduced only in patients with transferrin saturation less than 16% or ferritin less than 20 ng/mL at baseline.[32]

Preoperative rhEPO therapy without ABD is particularly indicated in patients with an anticipated need of approximately 2 U of allogeneic packed RBCs. According to our results, approximately 50% of patients with preoperative Hct levels of ≤0.45 are likely to require transfusion. This figure can be reduced to about 10% by a 2-week treatment with epoetin beta. Treatment should be discontinued if the Hct rises to greater than 0.50, since no additional benefit would be achieved and unnecessarily high Hct levels and greater treatment costs can be thus be avoided. Based on a standard patient (70 kg BW), the epoetin beta treatment according to our regimen costs $1,750 (assuming an American price level of $10 per 1,000 U rhEPO). Future studies should investigate whether a reduction in the need for ABT to approximately 10% can also be achieved with a reduced rhEPO dose and administration frequency by commencing treatment at an earlier stage, eg, from the twenty-first preoperative day. A further reduction in the ABT rate to less than 10% would be difficult to achieve, since very high blood losses from surgical complications cannot be offset by blood-saving measures.

The technique described in this trial for avoiding ABT in patients normally expected to require 2 transfused units of packed RBCs represents a favorable alternative to multiple ABD, with or without epoetin beta therapy. A similar transfusion requirement was found by Bidstrup et al in 671 cardiac surgical patients (41 institutions; median transfusion volume, 2.0 U per patient) without preoperative rhEPO therapy.[4] The results of our trial (42% of the placebo patients received 2 U of packed RBCs compared with 11% of the epoetin beta patients who needed ≥1 U) suggest that a perioperative transfusion requirement of 2 U can be avoided in three of four patients using the rhEPO treatment schedule investigated. We are convinced, therefore, that the saving of 2 U of packed RBCs represents an excellent result. The preoperative rhEPO therapy could possibly lead to savings in terms of personnel, time, and the collection and storage facilities required for multiple autologous blood donations. The patient retains his own endogenous erythrocyte reserves at the time of surgery. An additional benefit of our treatment regimen could be the reduced mental stress for the patient during the preoperative preparations. These conclusions need to be backed up by objective data obtained from future studies. Such investigations would have to show whether the preoperative rhEPO therapy without ABD was of importance in all elective surgical procedures, not just for the avoidance of ABT in heart surgery.

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