Effect of Single Recombinant Human Erythropoietin Injection on Transfusion Requirements in Preoperatively Anemic Patients Undergoing Valvular Heart Surgery

Young-Chul Yoo, M.D.,* Jae-Kwang Shim, M.D., Ph.D.,† Jong-Chan Kim, M.D.,‡ Youn-Yi Jo, M.D.,* Jong-Hoon Lee, M.D.,§ Young-Lan Kwak, M.D., Ph.D.‖

ABSTRACT

Background: The authors investigated the effect of a single preoperative bolus of erythropoietin on perioperative transfusion requirement and erythropoiesis in patients with preoperative anemia undergoing valvular heart surgery.

Methods: In this prospective, single-site, single-blinded, randomized, and parallel-arm controlled trial, 74 patients with preoperative anemia were randomly allocated to either the erythropoietin or the control group. The erythropoietin group received 500 IU/kg erythropoietin and 200 mg iron sucrose intravenously 1 day before the surgery. The control group received an equivalent volume of normal saline. The primary endpoint was transfusion requirement assessed during the surgery and for 4 days postoperatively. Reticulocyte count and iron profiles were measured serially and compared preoperatively and on postoperative days 1, 2, 4, and 7.

Results: Transfusion occurred in 32 patients (86%) of the control group *versus* 22 patients (59%) of the erythropoietin group ($P = 0.009$). The mean number of units of packed erythrocytes transfused per patient during the surgery and for 4 postoperative days (mean ± SD) was also significantly decreased in the erythropoietin group compared with the control group (3.3 ± 2.2 *vs.*. 1.0 ± 1.1 units/patient, $P = 0.001$). The reticulocyte count was significantly greater in the erythropoietin group at postoperative days 4 ($P = 0.001$) and 7 ($P = 0.001$).

Conclusions: A single intravenous administration of erythropoietin and an iron supplement 1 day before surgery significantly reduced the perioperative transfusion requirement in anemic patients undergoing valvular heart surgery, implicating its potential role as a blood conservation strategy.

What We Already Know about This Topic

- Blood transfusion carries many risks beyond transmission of infectious diseases, including major morbidity and mortality
- Avoiding transfusion by increasing endogenous erythrocyte production could also avoid these complications

What This Article Tells Us That Is New

- A single intravenous administration of erythropoietin and an iron supplement 1 day before surgery significantly reduced the perioperative transfusion requirement in anemic patients undergoing valvular heart surgery, implicating its potential role as a blood conservation strategy

CARDIAC surgery using cardiopulmonary bypass (CPB) poses a major hemostatic challenge frequently requiring transfusion of allogeneic blood products.[1] However, blood transfusion carries risks far beyond transmission of infectious diseases and has been clearly demonstrated to be

* Assistant Clinical Research Professor, † Associate Professor, ‡ Assistant Clinical Professor, Department of Anesthesiology and Pain Medicine, Anesthesia and Pain Research Institute, Yonsei University Health System, Seoul, Korea. § Resident, Department of Anesthesiology and Pain Medicine, Yonsei University Health System. ‖ Professor, Severance Biomedical Science Institute, Department of Anesthesiology and Pain Medicine, Anesthesia and Pain Research Institute, Yonsei University Health System.

Received from Yonsei University Health System, Seoul, Korea. Submitted for publication December 1, 2010. Accepted for publication July 5, 2011. Support was provided solely from institutional and/or departmental sources.

Address correspondence to Dr. Kwak: Severance Biomedical Science Institute, Department of Anesthesiology and Pain Medicine, Anesthesia and Pain Research Institute, Yonsei University Health System, 250 Seongsanno, Seodaemun-gu, Seoul 120-752, Korea. ylkwak@yuhs.ac. Anesthesiology 2011; 115:929–37

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◆ This article is accompanied by an Editorial View. Please see: Fox AA: Recombinant human erythropoietin: Efficacy and safety considerations for maximizing blood conservation in cardiac surgery. ANESTHESIOLOGY 2011; 115:912–4.

associated with adverse outcomes related to postoperative acute kidney injury, neurologic complication, atrial fibrillation, acute lung injury, and increased mortality.[2–6] Thus, the importance of blood conservation strategies to minimize transfusion is being increasingly emphasized.[7]

Recombinant human erythropoietin (rHuEPO) was developed to treat the anemia associated with reduced erythropoiesis caused by chronic renal disease and some hematologic diseases.[8,9] Several studies have demonstrated the efficacy of preoperative rHuEPO administration for cardiac surgery to restore erythrocyte transfusion in patients having autologous blood donations.[10,11] rHuEPO has also been demonstrated to be safe and effective to improve preoperative anemia, and it can be used in conjunction with iron therapy in patients with hemoglobin concentrations less than 13 g/dl.[12,13] However, a typical preoperative regimen of rHuEPO is costly and requires at least 4 days of hospitalization before the surgery, limiting the more widespread use of this strategy.[1] Outpatient-based repeated injections of rHuEPO *via* the subcutaneous route may be feasible[12]; however, it may be related to the increased occurrence of therapy-related complications such as hypertension and thromboembolism.[14] In addition, the absorption of subcutaneously administered rHuEPO may not be consistent and reliable compared with the intravenous route due to decreased microcirculation in patients with cardiac disease.[15]

During the postoperative period, the decrease in hemoglobin concentration in the absence of further blood loss is accompanied by a state of relative hypoferremia with a blunted increase in the concentration of erythropoietin and reticulocytes persisting for more than 1 week and mediated by the ensuing systemic inflammatory response.[16–19] Therefore, in the context of optimizing inpatient procedures, switching the target of rHuEPO therapy from increasing the preoperative hemoglobin concentration to potentially mitigating the inflammatory response-induced blunted erythropoiesis would greatly reduce the related cost without influencing the duration of preoperative hospitalization. Considering that the inflammatory response initiates with the induction of anesthesia, a single preemptive intravenous bolus of rHuEPO with iron supplementation could result in enhanced postoperative erythropoiesis and the reduced requirement for transfusion. This single dose approach was demonstrated to be effective in terms of hemoglobin concentration and transfusion requirement immediately from postoperative day (POD) 1 in orthopedic surgical patients,[20] yet no comprehensive data exist to support this hypothesis.

We designed this prospective single-site, single-blinded, randomized, and parallel-arm controlled trial to investigate the effect of a single preoperative intravenous bolus of rHuEPO on perioperative transfusion requirement in patients with preoperative anemia undergoing valvular heart surgery (VHS). The primary endpoint was to compare perioperative transfusion requirement in terms of overall incidence and mean number of units of packed erythrocytes transfused per patient during the surgery and for 4 days after surgery. Secondary endpoints were comparisons of daily transfusion requirement during the postoperative period until the fourth POD, serial changes of hemoglobin concentration, reticulocyte count, iron profiles, and occurrence of postoperative complications.

Materials and Methods

Patients

This trial was conducted at Yonsei University Health System, Seoul, Korea between April 2009 and April 2010. The study protocol was approved by the Institutional Review Board of Severance Hospital, Yonsei University Health System and was performed in full compliance with the Declaration of Helsinki. Participants were recruited from the Anesthesiology Preoperative Evaluation Clinic and gave written informed consent. Seventy-four patients scheduled for VHS and who had preoperative anemia were enrolled. Patients were randomly allocated to either the rHuEPO or the control group in a 1:1 ratio by means of computer-generated random numbers. A ward physician not involved in the current trial performed randomization and assignment. We defined anemia as a hemoglobin concentration less than 12 g/dl in women and less than 13 g/dl in men according to World Health Organization criteria.[21] Patients with preexisting uncontrolled hypertension (diastolic blood pressure more than 100 mmHg), platelet count more than 450,000/mm^3, history of thromboembolism, seizure, malignant disease, liver dysfunction, confirmed renal impairment (serum creatinine [Cr] >2 mg/dl), aplastic or iron deficiency anemia and/or acute hyperparathyroidism, and hypersensitivity to iron therapy were excluded.

Treatment

Patients in the rHuEPO group received 500 IU/kg rHuEPO (Epocain prefilled, CJ Pharma Co., Ltd., Seoul, Korea) *via* intravenous bolus administration at 16–24 h before surgery. At the same time, 200 mg iron sucrose supplement (Venoferrum, BYK Gulden, Inc, Singen, Germany) mixed with 100 ml normal saline was administered intravenously for 1 h. The patients in the control group received an equivalent volume of normal saline for the same duration without iron supplementation. Medications were prepared and administered by a ward physician recognizing the patient's group but not involved in the current study, whereas the surgeon and anesthesiologist involved in the study and patient management were blinded to the patients' groups until the end of the study.

Clinical Evaluations

Primary endpoints were comparisons of perioperative transfusion requirement in terms of overall incidence and mean number of units of packed erythrocytes transfused per patient during the operation and for 4 PODs. Secondary end-

points were comparisons of daily packed erythrocytes requirement during the postoperative period until the fourth POD, serial changes of hemoglobin concentration, reticulocyte count, iron profiles, and occurrence of postoperative complications. At our institution the mediastinal tube is usually removed 4 days after surgery. We followed up on the amount of allogeneic packed erythrocytes transfusions and bleeding up to POD 4. Hemoglobin concentration less than 7 mg/dl during CPB, and less than 8 mg/dl after CPB and postoperatively, were used as transfusion thresholds. Intraoperatively, we measured the hemoglobin concentration postinduction and every 30 min during CPB, then at 10 min post-CPB and poststernal closure, and postoperatively at the time of and 8 h after arrival at the intensive care unit. After the day of surgery, we measured the hemoglobin concentration once in the morning if there was no excessive bleeding or symptoms of anemia. The patients who had hemoglobin concentrations higher than 8 mg/dl postoperatively, yet required transfusion due to symptoms of acute anemia such as shortness of breath, change in respiratory rate and pulse rate, mental function deterioration, and myocardial ischemia were excluded from the study.[22]

Preoperative variables included demographic data, type of surgery, comorbid conditions (including presence of diabetes mellitus, hypertension, chronic renal failure, cerebrovascular accidents, and/or congestive heart failure), and medications. We also measured the risk of early mortality in patients undergoing cardiac surgery by the logistic EuroSCORE.[23] Intraoperative variables included anesthesia time, duration of aortic cross clamp and CPB, fluid balance including blood, fluid, and cell saver input, and urine output. Postoperative variables included the amount of bleeding measured by chest tube drainage for 4 days after surgery, fluid input, urine output, and amount of allogeneic blood transfusion. Hemoglobin concentrations were measured preoperatively, at postanesthetic induction, and POD 0 (day of the surgery after arrival in the intensive care unit), 1, 2, 3, 4, and 7. Reticulocyte count and iron profiles including serum iron concentrations, total iron binding capacity, and ferritin concentrations, and transferrin saturation were measured preoperatively and at postanesthetic induction and POD 1, 2, and 7, and the changes in reticulocyte count from the baseline values (Δ reticulocyte count) were calculated. Postoperative variables also included the incidence of perioperative multiple allogeneic transfusion, incidence of acute kidney injury (AKI) within 48 h after surgery, atrial fibrillation for 7 days after surgery, duration of ventilator care, intensive care unit stay and hospital stay, and in-hospital mortality. Multiple allogeneic transfusion was defined as transfusion of more than 1 unit of packed erythrocytes during the operation and for 4 PODs. AKI was defined as elevation of serum Cr of $\geq$0.3 mg/dl or 50–200% from baseline using modified Risk, Injury, Failure, Loss, and End-stage Kidney Disease classification.[24,25] Surgical mortality was defined as all deaths that occurred during the hospital stay or after hospital discharge but within 30 days postoperatively. Possible complications associated with rHuEPO therapy such as hypertension, thromboembolism, headache, tachycardia, nausea, vomiting, hypercalcemia, and diarrhea were also assessed from the beginning of the administration of rHuEPO until hospital discharge. Although our study was not designed to validate the difference in outcome variables such as AKI, atrial fibrillation, duration of ventilator care, intensive care unit, and hospital stay, and surgical mortality, it could be informative to provide postoperative outcome variables to demonstrate that erythropoietin therapy did not appear to be associated with adverse outcome.

Perioperative Management

All patients were premedicated with 0.05 mg/kg intramuscular morphine 1 h before arriving in the operating room. Five electrocardiogram leads were attached, and leads II and V_5 were continuously monitored. A 20-G radial artery catheter was inserted under local anesthesia. For continuous cardiac output monitoring, a thermodilutional pulmonary artery catheter (Swan-Ganz, CCOmbo, Baxter Healthcare Co., Irvine, CA) was inserted *via* the right internal jugular vein under local anesthesia. After that, anesthesia was induced with 0.05 mg/kg midazolam, 1.5 μg/kg sufentanil, and 50 mg rocuronium, and maintained with continuous infusion of sufentanil at 0.5 $\mu g \cdot kg^{-1} \cdot h^{-1}$, vecuronium at 8–10 mg/h, and a low dose of sevoflurane in oxygen (40–60%) with air during the surgery. A transesophageal echocardiographic probe was inserted to monitor global myocardial function and assess the replaced valves. Arterial oxygen saturation, end-expiratory sevoflurane concentration, and nasopharyngeal and rectal temperatures were monitored during the study. Mechanical ventilation was controlled to maintain normocapnia. The depth of anesthesia was monitored with a Bispectral Index score monitor (A-200 Bispectral Index® score monitor, Aspect Medical System Inc., Newton, MA) and maintained at 40–60. Any mean arterial pressure less than 60 mmHg was treated with norepinephrine. CPB was instituted with a membrane oxygenator primed with 1.6 l priming solution, which consisted of 100 ml 20% human albumin, 20% mannitol (5 ml/kg), $NaHCO_3$ (20 mEq), heparin (2,000 IU), sufentanil 1.5 μg/kg, midazolam 0.05 mg/kg, and acetated Ringer's solution (Plasma Solution A Inj., CJ Pharma, Seoul, Korea). Body temperature was cooled to 32–33°C. A nonpulsatile pump flow rate was maintained at 2.0–2.5 $l \cdot min^{-1} \cdot m^{-2}$. During the period before and after CPB, crystalloid solution was infused at a fixed rate of 6–8 $ml \cdot kg^{-1} \cdot h^{-1}$, whereas colloid solution (Voluven®, Fresenius Kabi, Bad Homburg, Germany) was infused to compensate for the amount of blood loss at a maximal dose of 20 $mg \cdot kg^{-1} \cdot day^{-1}$. All patients received a loading dose of 1 g tranexamic acid followed by an infusion of 200 mg/h during the surgery, and another loading dose of 1g with the onset of CPB. Blood salvaged by the cell salvage device was reinfused into the patient before the end of surgery. This trial was overseen by an independent

data safety monitoring board. The independent committee had reviewed our data when 15%, 33%, and 66% of the anticipated number of patients were accumulated for ensuring safe and ethical treatment of research participants, data quality, and credibility of study findings.

Statistical Analysis

Continuous variables were shown as means ± SD and dichotomous variables were shown as numbers (percentages). Between-group comparisons of continuous variables were performed by independent Student *t* test. Dichotomous variables were compared using chi-square or Fisher exact tests, as appropriate. Hemoglobin, reticulocyte count, and iron profiles were analyzed using a linear mixed model with patient indicator as a random effect, group, time, and group-by-time as fixed effects. All statistical tests were two-tailed. *P* values less than 0.05 were considered statistically significant. This study was designed to validate the superiority of rHuEPO treatment. In a previous study using aprotinin,[26] the transfusion rate in the control group was 44%. A power estimation analysis of that study suggested that 32 patients per group would be required to obtain a power of 80%, considering a type I error of 0.05, and expecting a reduction from 44% to 13% in the incidence of allogeneic erythrocyte transfusion. All statistical analyses were performed using SPSS software version 15.0 (SPSS Inc., Chicago, IL).

Results

VHS could be performed as planned in all patients, and complete data sets from the 74 patients were analyzed without any missing data.

Patients' characteristics and performed surgeries were similar between the groups (table 1). There were no patients with hemoglobin concentrations higher than 8 mg/dl and symptoms such as shortness of breath, change in respiratory rate and pulse, mental function deterioration, and myocardial ischemia, although that would have required transfusion.

Surgical characteristics including anesthesia time, duration of aortic cross clamp and CPB, and fluid balance including the amount of ultrafiltration were similar between the groups (table 2).

During the perioperative period combining the values during surgery and 4PODs, the mean number of units of packed erythrocytes transfused per patient (3.3 ± 2.2 *vs.* 1.0 ± 1.1 units/patient, $P = 0.001$), mean number of units of packed erythrocytes transfused per transfused patient (3.7 ± 2.1 *vs.* 1.6 ± 0.9 units/patient who received erythrocyte transfusion, $P = 0.004$), and number of patients transfused with allogeneic erythrocyte (32 *vs.* 22, $P = 0.009$) were significantly less in the rHuEPO group. In detail, the number of patients transfused with erythrocyte during surgery was similar between the groups, whereas the mean number of units of packed erythrocytes transfused per patient during surgery was significantly greater in the control group. During the postoperative period, the amount of blood loss was similar between the groups. In contrast, the mean number of units of packed erythrocytes transfused per patient and the number of patients transfused with allogeneic erythrocyte at POD 0, 1–2, and 3–4, and during 4 PODs were significantly less in the rHuEPO group (table 3). Total amounts of fluid input and urine output during 4 PODs were similar between the groups.

The lowest postoperative hemoglobin concentrations were significantly higher in the rHuEPO group at PODs 2, 3, and 4. Reticulocyte count at PODs 4 and 7, and Δ reticu-

Table 1. Patient Demographics and Preoperative Clinical Data

	Control (n = 37)	rHuEPO (n = 37)	*P* Value
Age (yr)	59 ± 12	56 ± 12	0.208
Female sex	23 (62.2)	24 (64.9)	0.809
BMI (kg/m^2)	23 ± 4	23 ± 3	0.994
Operation			
AVR	16 (41.7)	12 (31.4)	0.338
MVR	14 (37.8)	14 (37.8)	0.999
DVR	5 (13.5)	4 (10.8)	0.722
Valve + CABG	0 (0)	2 (5.4)	0.493
Bental	2 (5.4)	5 (13.5)	0.430
Redo	3 (8.1)	1 (2.7)	0.615
DM	3 (8.1)	7 (18.9)	0.308
Hypertension	14 (37.8)	9 (24.3)	0.209
CVA	2 (5.4)	1 (2.7)	0.999
CHF	2 (5.4)	1 (2.7)	0.999
Medications			
β−blockers	15 (41.7)	8 (21.6)	0.065
CCB	6 (16.7)	5 (13.5)	0.707
ACEi	10 (27.8)	8 (21.6)	0.542
ARB	9 (25)	10 (27)	0.844
Diuretics	17 (50)	17 (50)	0.913
EuroSCORE	3.6 ± 2.2	3.9 ± 2.3	0.538

Values are mean ± SD or number of patients (%).

ACEi = angiotensin-converting enzyme inhibitor; ARB = angiotensin receptor blocker; AVR = aortic valve replacement; BMI = body mass index; CCB = calcium channel blockers; CHF = congestive heart failure; CVA = cerebrovascular accident; DM = diabetes mellitus; DVR = double valve replacement; MVR = mitral valve replacement; rHuEPO = recombinant human erythropoietin; Valve + CABG = valvular replacement with coronary artery bypass grafting.

Table 2. Intraoperative Parameters

	Control (n = 37)	rHuEPO (n = 37)	*P* Value
Anesthesia time (min)	293 ± 76	289 ± 66	0.800
ACC time (min)	85 ± 26	82 ± 33	0.770
CPB time (min)	115 ± 35	113 ± 40	0.940
Fluid balance			
Crystalloid (ml)	1,731 ± 917	1,763 ± 846	0.850
Colloid (ml)	685 ± 454	630 ± 306	0.564
Urine output (ml)	1,018 ± 689	1,165 ± 964	0.451

Values are mean ± SD.

ACC time = duration of aortic cross clamp; CPB time = duration of cardiopulmonary bypass; rHuEPO = reombinant human erythropoietin.

Table 3. Perioperative Transfusion Requirement and Postoperative Blood Loss

	Group	Intra-Operative	POD 0	POD 1–2	POD 3–4	Postoperative Total	Perioperative Total
Amount of blood loss (ml)	Control		321 ± 287	366 ± 305	79 ± 248	766 ± 558	
	rHuEPO		307 ± 276	301 ± 206	19 ± 41	624 ± 380	
Amount of erythrocytes (units/patient)	Control	1.2 ± 1.1	0.9 ± 1.1	0.8 ± 1.3	0.4 ± 0.9	2.1 ± 1.9	3.3 ± 2.2
	rHuEPO	0.7 ± 0.7*	0.2 ± 0.6*	0.1 ± 0.3*	0 ± 0*	0.3 ± 0.8*	1.0 ± 1.1*
Amount of erythrocytes/ transfused patients (units/transfused patient)	Control	1.7 ± 1.0	1.7 ± 1.1	2.6 ± 1.0	2.0 ± 0.9	2.8 ± 1.8	3.7 ± 2.1
	rHuEPO	1.4 ± 0.6	1.6 ± 0.9	2		2.0 ± 1.4	1.6 ± 0.9*
Patients transfused with erythrocytes (n)	Control	25 (67.7)	20 (54.1)	10 (27)	8 (21.6)	27 (73)	32 (86.5)
	rHuEPO	20 (54.1)	5 (13.5)*	1 (2.7)*	0 (0)*	5 (13.5)*	22 (59.5)*
Mean hemoglobin concentrations (mg/dl)	Control		9.0 ± 0.8	8.8 ± 1.0	8.7 ± 0.8		
	rHuEPO		9.3 ± 1.0	9.3 ± 0.9*	9.0 ± 0.8		

Values are mean ± SD or number of patients (%).

* $P < 0.05$ *vs.* control group.

Amount of erythrocytes = number of units of erythrocytes transfused for the entire study group divided by the total number of subjects in that study group; Amount of erythrocytes/transfused patients = number of units of erythrocytes transfused for the entire study group divided by the number of transfused patients in that study group; Perioperative = intraoperative plus postoperative; POD = postoperative day; POD 0 = day of the surgery after arrival in the intensive care unit; rHuEPO = recombinant human erythropoietin.

locyte count at PODs 2, 4, and 7 were significantly higher in the rHuEPO group (table 4). After additional adjustment for β-blocker use in our between-group comparisons of reticulocyte response over time using linear mixed model assessment, the results were not different from presented analysis.

Serum iron concentrations, total iron binding capacity, and ferritin and transferrin saturation were similar between the groups, with the exception of significantly higher serum iron and transferrin saturation after anesthetic induction in the rHuEPO group (fig. 1).

During the postoperative period, significantly fewer patients received multiple transfusions in the rHuEPO group. The number of patients who developed AKI was also significantly less in the rHuEPO group. The duration of ventilator care and intensive care unit stay demonstrated trends toward being shorter in the rHuEPO group without statistical significance. Other variables including the mortality rate were not different between the groups (table 5).

In both groups, there were no patients who developed complications associated with rHuEPO therapy such as hypertension, headache, tachycardia, nausea, vomiting, hypercalcemia, and diarrhea.

Discussion

In this randomized controlled trial addressing the efficacy of a single preemptive dose of rHuEPO and iron supplementation at 1 day before VHS on reducing transfusion requirement in patients with preoperative anemia, we observed a statistically significant reduction in the number of patients requiring trans-

Table 4. Changes of Hematopoietic Factors

Group	Preoperative	Post Induction	POD 0	POD 1	POD 2	POD 3	POD 4	POD 7
Hemoglobin (g/dl)								
Control	11.6 ± 1.2	11.5 ± 1.4	9 ± 1†	8.8 ± 1.2†	8.4 ± 0.9†	8.2 ± 0.9†	8.3 ± 1.1†	9.4 ± 1.3†
rHuEPO	11.8 ± 0.8	11.6 ± 1.2	9.4 ± 1.3†	9.5 ± 1.0†	9.4 ± 0.8*†	9.3 ± 0.7*†	9.4 ± 0.9*†	9.5 ± 1.0†
Reticulocyte count ($10^3/\mu l$)								
Control	73 ± 30	75 ± 27		61 ± 22	64 ± 26		68 ± 28	105 ± 45†
rHuEPO	70 ± 26	80 ± 24		72 ± 24	73 ± 23		92 ± 25*†	164 ± 52*†
Δ Reticulocyte count ($10^3/\mu l$)								
Control		1 ± 14		–14 ± 16	–11 ± 22		0 ± 22	32 ± 44
rHuEPO		10 ± 13		–3 ± 18	0 ± 21*		13 ± 24*	93 ± 52*

Values are mean ± SD. Hemoglobin concentrations on POD 0 to POD 7 are the lowest values among evaluations taken each day.

* $P < 0.05$ *vs.* control group; † $P < 0.05$ *vs.* baseline value.

POD = postoperative day; POD 0 = day of the surgery after arrival in the intensive care unit; rHuEPO = recombinant human erythropoietin; Δ Reticulocyte count = change in reticulocyte count from the preoperative values.

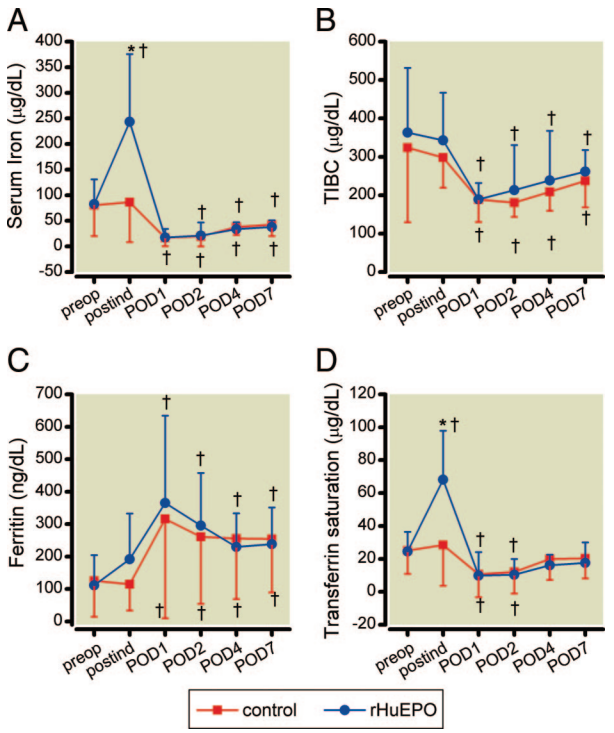


Fig. 1. Changes of serum iron (*A*), TIBC (*B*), ferritin (*C*) concentrations, and transferrin saturation (*D*) over time in the control group and rHuEPO group. Values are mean ± SD. * $P < 0.05$ compared with the control group. † $P < 0.05$ compared with the baseline. POD = postoperative days; postind = postanesthetic induction; preop = preoperative; rHuEPO = recombinant human erythropoietin; TIBC = total iron binding capacity.

fusion as well as the mean number of units of packed erythrocytes transfused per patient during the perioperative period in the rHuEPO group. The degree of decrease in reticulocyte counts was less at PODs 2, 4, and 7 in the rHuEPO group compared with the control group, and enhancement of erythropoiesis was observed from POD 4 with statistical significance.

Allogeneic blood transfusion is a recognized risk factor for morbidity and mortality after cardiac surgery.[4,5] Despite efforts to reduce allogeneic blood transfusion, it remains common in cardiac surgery.[5] rHuEPO treatment with or without preoperative autologous blood donation is known to reduce allogeneic blood transfusion.[1,10–13] However, the requirement for repeated rHuEPO injections for an interval of several days was considered time-consuming and was associated with the potential risk of thromboembolic complications.

In addition to surgical bleeding and coagulopathy, postoperative anemia is aggravated by systemic inflammatory response-induced erythropoiesis inhibition.[16–19] Postoperative anemia is characterized as a relative erythropoietin- and iron-deficient state and a resultant serial reduction of hemoglobin concentrations for several days.[17] The degree of postoperative anemia due to inflammation is related to the extent of surgery.[18] Cardiac surgery using CPB would thus be presumed to be associated with more blunted erythropoiesis and interference of iron metabolism and to augment postoperative anemia more than noncardiac surgery would.[27] Several studies have aimed to determine whether the speed of recovery from postoperative anemia can be accelerated with postoperative rHuEPO treatment. During the postpartum period in patients with anemia, a single postoperative injection of rHuEPO was reported to activate blunted postoperative erythropoiesis and to effectively correct anemia.[28] However, postoperative use of rHuEPO failed to increase hemoglobin concentrations despite increased reticulocyte count in most studies.[17,29]

Recently, in an attempt to develop a more practical regimen, five rHuEPO injections for 2 days before off-pump coronary artery bypass surgery was reported to diminish postoperative allogeneic blood transfusions.[13] Another study reported a higher postoperative hemoglobin concentration after coronary artery bypass surgery by administering three doses of rHuEPO starting on the day before surgery. However, the primary endpoint of that study was to elucidate the neuroprotective effect of rHuEPO, and the sample size was too small to draw any conclusion in terms of blood conservation.[30] Yet, the role of preemptive single rHuEPO bolus therapy as a blood conservation strategy in preoperatively anemic patients undergoing cardiac surgery with CPB has not been comprehensively evaluated to date.

Because our primary objective was to validate the efficacy of a single dose of rHuEPO before the surgery without requiring additional hospital stays, we used a rather high single dosage, which was almost the highest dose of intravenously injected rHuEPO (500 IU/kg) that has been used in clinical studies.[10,31] Because we wanted to test the feasibility and efficacy of this regimen

Table 5. Postoperative Outcome

	Control (n = 37)	rHuEPO (n = 37)	*P* Value
Multiple transfusion, yes	20 (54.1)	5 (13.5)	0.0001
Postoperative AKI, yes	19/35 (54.3)	9/37 (24.3)	0.017
Postoperative AF, yes	9/30 (30)	6/28 (21.4)	0.456
Duration of ventilator care (h)	18.9 ± 8.9	16 ± 4.6	0.085
Duration of ICU stay (h)	68.1 ± 49.1	51.7 ± 21.5	0.068
Duration of hospital stay (days)	13.5 ± 8.0	11.3 ± 4.1	0.133
Death	1 (2.7)	0	

Values are mean ± SD.

AF = atrial fibrillation; AKI = acute kidney injury; Death = all deaths that occurred during the hospital stay or after hospital discharge but within 30 days postoperatively; ICU = intensive care unit; Multiple transfusion = transfusion of > 1 unit of packed erythrocytes during the operation and for 4 postoperative days; rHuEPO = recombinant human erythropoietin.

on reducing transfusion requirement within the timeframe of routine hospital admission policies for elective VHS at our institution, we administered rHuEPO at 1 day before the surgery.

Our data revealed that the transfusion requirement of allogeneic erythrocyte in the rHuEPO group during the perioperative as well as the postoperative period was statistically significantly reduced. Impressively, only a single patient required transfusion after the day of surgery in the rHuEPO group while several patients were repeatedly transfused during the postoperative period in the control group. rHuEPO treatment was accompanied by less of a reduction in reticulocyte count and statistically significant enhancement of erythropoiesis compared with the control group.

Regarding the treatment of temporarily depressed erythropoiesis, existing evidence supports the rapid beneficial hematologic effect of a single high dose of rHuEPO during the perioperative period. Reticulocyte counts have been demonstrated to readily increase after rHuEPO injection in a dose-dependent manner while a peak response occurred at 4 to 5 days after a single injection.[32] In that study, rHuEPO has been proposed to act on the mature erythroblasts to give rise to an early 24-h reticulocyte response. In our study, the increase in absolute reticulocyte counts compared with baseline values could be observed only at PODs 4 and 7 in the rHuEPO group, in accordance with most previous studies.[1,32] However, the Δ reticulocyte counts were constantly higher in the rHuEPO group, bearing statistical significance as early as POD 2, whereas no statistically significant increase in reticulocyte counts was observed until POD 7 in the control group. These findings support the role of single preemptive rHuEPO treatment in reduced transfusion requirement, because other known risk factors of transfusion were similar between the groups. Still, additional mechanisms accounting for the acute effect of rHuEPO on postoperative transfusion requirement should be investigated.

Although there was no statistical significance, more patients received β-blocker therapy in the control group, which could be a confounding factor because β-adrenergic agonists can stimulate erythropoietin secretion.[33] Therefore, we also adjusted for β-blocker use in our between-group comparisons of reticulocyte response over time using mixed linear model assessment; similar results were observed as in our presented analyses.

In the control group, cardiac surgery led to changes in iron metabolism such as a decrease in serum iron and transferrin saturation and an increase in serum ferritin concentration, in agreement with previous studies.[18] Because the amount of stored iron needed to replace 1 g/dl hemoglobin is 150 mg,[17] and inflammation decreases intestinal iron absorption,[34] we administered 200 mg iron intravenously. In the rHuEPO group, despite intravenous iron supplementation 1 day before the surgery, the serum iron concentration and transferrin saturation increased only during the postinduction period. This may be associated with the fact that supplied iron is rapidly cleared during increased erythropoiesis with an erythrocyte uptake of 80–90%.[35]

Several studies have suggested that erythropoietin has protective action against ischemia-reperfusion injury in the kidney, heart, and brain.[36] A recent clinical study reported that administration of 300 IU/kg rHuEPO to patients undergoing coronary artery bypass surgery reduced the incidence of AKI and improved postoperative renal function, although information for allogeneic blood transfusion was unclear.[37] Interestingly, the number of patients who developed AKI was less in the rHuEPO group in our study, with statistical significance. However, because transfusion is an independent risk factor for AKI after cardiac surgery[38] and the transfusion rate was lower in the rHuEPO group, it is unclear whether preserved postoperative renal function is due to a renoprotective effect of rHuEPO. We also noted distinct trends toward shorter duration of ICU stay and hospitalization in the rHuEPO group. Our study was not designed to validate the beneficial effects of rHuEPO therapy on postoperative outcome, and this subject merits further studies with a proper sample size.

The possible complications of rHuEPO therapy include hypertension, headache, tachycardia, nausea, vomiting, hypercalcemia, diarrhea, and thromboembolic complication. However, these complications usually occur in patients who receive chronic, repeated erythropoietin therapy.[1,12] More importantly, chronic use in cancer patients is associated with increased thrombotic risk, but short-term use for acute indications currently appears to be safe, even in critically ill patients.[31,39] In addition, thromboembolic complication is known to be proportional to the blood hemoglobin concentration,[40] while we enrolled preoperatively anemic patients for whom preoperative use of rHuEPO was reported to be most beneficial.[15] Although complete correction of anemia might accentuate vasoconstriction and increase blood pressure and the risk of thrombosis,[41] our study was not targeted to correct preoperative anemia, and none of the patients had hemoglobin concentrations above 12 g/dl throughout the study period. Accordingly, none of the patients experienced any complications. Our study demonstrated the safety of a large preemptive single intravenous dose of rHuEPO.

The limitations of this study are as follows. The theoretic background selecting the timing of rHuEPO administration in this study was based on the assumption that a preemptive single dose of rHuEPO may mitigate the inflammatory response-induced blunted erythropoiesis. However, this hypothesis remains speculative because we did not evaluate the representative inflammatory markers. Although we excluded patients with iron deficiency anemia, a relative iron-deficient state occurs during the postoperative period.[17] Therefore, iron supplementation alone may have influenced the result, which was not given in the control group.

In conclusion, a single 500 IU/kg intravenous rHuEPO injection and concomitant iron supplementation 1 day before surgery resulted in statistically significant reduction of perioperative transfusion requirement in anemic patients undergoing VHS. Given the lack of complications of our treatment protocol and its compatibility with current inpatient optimization procedures, it should be considered as a promising blood conservation strategy in patients with preoperative anemia who are undergoing VHS.

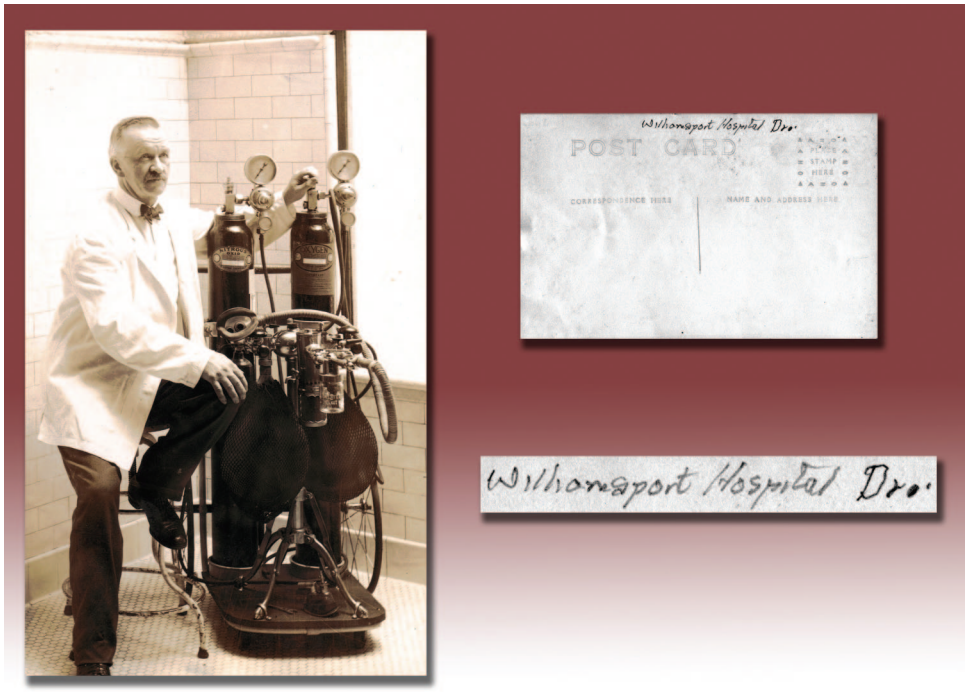
References

1. Yaziciolu L, Eryilmaz S, Sirlak M, Inan MB, Aral AR, Eren NT, Kaya B, Akalin H: Recombinant human erythropoietin administration in cardiac surgery. J Thorac Cardiovasc Surg 2001; 122:741–5
2. De Santo LS, Romano G, Galdieri N, Buonocore M, Bancone C, De Simone V, Della Corte A, Nappi G: RIFLE criteria for acute kidney injury in valvular surgery. J Heart Valve Dis 2010; 19:139–47; discussion 148
3. Bucerius J, Gummert JF, Borger MA, Walther T, Doll N, Onnasch JF, Metz S, Falk V, Mohr FW: Stroke after cardiac surgery: A risk factor analysis of 16,184 consecutive adult patients. Ann Thorac Surg 2003; 75:472–8
4. Koch CG, Li L, Van Wagoner DR, Duncan AI, Gillinov AM, Blackstone EH: Red cell transfusion is associated with an increased risk for postoperative atrial fibrillation. Ann Thorac Surg 2006; 82:1747–56
5. Scott BH, Seifert FC, Grimson R: Blood transfusion is associated with increased resource utilisation, morbidity and mortality in cardiac surgery. Ann Card Anaesth 2008; 11:15–9
6. Surgenor SD, Kramer RS, Olmstead EM, Ross CS, Sellke FW, Likosky DS, Marrin CA, Helm RE Jr, Leavitt BJ, Morton JR, Charlesworth DC, Clough RA, Hernandez F, Frumiento C, Benak A, DioData C, O'Connor GT, Northern New England Cardiovascular Disease Study Group: The association of perioperative red blood cell transfusions and decreased long-term survival after cardiac surgery. Anesth Analg 2009; 108:1741–6
7. Kulier A, Levin J, Moser R, Rumpold-Seitlinger G, Tudor IC, Snyder-Ramos SA, Moehnle P, Mangano DT, Investigators of the Multicenter Study of Perioperative Ischemia Research Group, Ischemia Research and Education Foundation: Impact of preoperative anemia on outcome in patients undergoing coronary artery bypass graft surgery. Circulation 2007; 116:471–9
8. Jacobs K, Shoemaker C, Rudersdorf R, Neill SD, Kaufman RJ, Mufson A, Seehra J, Jones SS, Hewick R, Fritsch EF: Isolation and characterization of genomic and cDNA clones of human erythropoietin. Nature 1985; 313:806–10
9. Rizzo JD, Somerfield MR, Hagerty KL, Seidenfeld J, Bohlius J, Bennett CL, Cella DF, Djulbegovic B, Goode MJ, Jakubowski AA, Rarick MU, Regan DH, Lichtin AE: Use of epoetin and darbepoetin in patients with cancer: 2007 American Society of Hematology/American Society of Clinical Oncology clinical practice guideline update. Blood 2008; 111:25–41
10. Kiyama H, Ohshima N, Imazeki T, Yamada T: Autologous blood donation with recombinant human erythropoietin in anemic patients. Ann Thorac Surg 1999; 68:1652–6
11. Gombotz H: Subcutaneous epoetin alfa as an adjunct to autologous blood donation before elective coronary artery bypass graft surgery. Semin Hematol 1996; 33:69–70; discussion 71–2
12. Alghamdi AA, Albanna MJ, Guru V, Brister SJ: Does the use of erythropoietin reduce the risk of exposure to allogeneic blood transfusion in cardiac surgery? A systematic review and meta-analysis. J Card Surg 2006; 21:320–6
13. Weltert L, D'Alessandro S, Nardella S, Girola F, Bellisario A, Maselli D, De Paulis R: Preoperative very short-term, high-dose erythropoietin administration diminishes blood transfusion rate in off-pump coronary artery bypass: A randomized blind controlled study. J Thorac Cardiovasc Surg 2010; 139: 621–6; discussion 626–7
14. Lippi G, Franchini M, Favaloro EJ: Thrombotic complications of erythropoiesis-stimulating agents. Semin Thromb Hemost 2010; 36:537–49
15. Sowade O, Warnke H, Scigalla P, Sowade B, Franke W, Messinger D, Gross J: Avoidance of allogeneic blood transfusions by treatment with epoetin beta (recombinant human erythropoietin) in patients undergoing open-heart surgery. Blood 1997; 89:411–8
16. Biesma DH, Van de Wiel A, Beguin Y, Kraaijenhagen RJ, Marx JJ: Post-operative erythropoiesis is limited by the inflammatory effect of surgery on iron metabolism. Eur J Clin Invest 1995; 25:383–9
17. Karkouti K, McCluskey SA, Ghannam M, Salpeter MJ, Quirt I, Yau TM: Intravenous iron and recombinant erythropoietin for the treatment of postoperative anemia. Can J Anaesth 2006; 53:11–9
18. van Iperen CE, Kraaijenhagen RJ, Biesma DH, Beguin Y, Marx JJ, van de Wiel A: Iron metabolism and erythropoiesis after surgery. Br J Surg 1998; 85:41–5
19. Clemens J, Spivak JL: Serum immunoreactive erythropoietin during the perioperative period. Surgery 1994; 115:510–5
20. Na HS, Shin SY, Hwang JY, Jeon YT, Kim CS, Do SH: Effects of intravenous iron combined with low-dose recombinant human erythropoietin on transfusion requirements in iron-deficient patients undergoing bilateral total knee replacement arthroplasty. Transfusion 2011; 51:118–24
21. Goodnough LT, Shander A, Spivak JL, Waters JH, Friedman AJ, Carson JL, Keating EM, Maddox T, Spence R: Detection, evaluation, and management of anemia in the elective surgical patient. Anesth Analg 2005; 101:1858–61
22. Murphy MF, Wallington TB, Kelsey P, Boulton F, Bruce M, Cohen H, Duguid J, Knowles SM, Poole G, Williamson LM, British Committee for Standards in Haematology, Blood Transfusion Task Force: Guidelines for the clinical use of red cell transfusions. Br J Haematol 2001; 113:24–31
23. Roques F, Michel P, Goldstone AR, Nashef SA: The logistic EuroSCORE. Eur Heart J 2003; 24:881–2
24. Molitoris BA, Levin A, Warnock DG, Joannidis M, Mehta RL, Kellum JA, Ronco C, Shah S, Acute Kidney Injury Network: Improving outcomes from acute kidney injury. J Am Soc Nephrol 2007; 18:1992–4
25. Hoste EA, Kellum JA: Acute kidney injury: Epidemiology and diagnostic criteria. Curr Opin Crit Care 2006; 12:531–7
26. Diprose P, Herbertson MJ, O'Shaughnessy D, Deakin CD, Gill RS: Reducing allogeneic transfusion in cardiac surgery: A randomized double-blind placebo-controlled trial of antifibrinolytic therapies used in addition to intra-operative cell salvage. Br J Anaesth 2005; 94:271–8
27. Wehlin L, Vedin J, Vaage J, Lundahl J: Activation of complement and leukocyte receptors during on- and off pump coronary artery bypass surgery. Eur J Cardiothorac Surg 2004; 25:35–42
28. Breymann C, Zimmermann R, Huch R, Huch A: Use of recombinant human erythropoietin in combination with parenteral iron in the treatment of postpartum anaemia. Eur J Clin Invest 1996; 26:123–30
29. Madi-Jebara SN, Sleilaty GS, Achouh PE, Yazigi AG, Haddad FA, Hayek GM, Antakly MC, Jebara VA: Postoperative intravenous iron used alone or in combination with low-dose erythropoietin is not effective for correction of anemia after cardiac surgery. J Cardiothorac Vasc Anesth 2004; 18:59–63
30. Haljan G, Maitland A, Buchan A, Arora RC, King M, Haigh J, Culleton B, Faris P, Zygun D: The erythropoietin neuroprotective effect: Assessment in CABG surgery (TENPEAKS): A randomized, double-blind, placebo controlled, proof-of-concept clinical trial. Stroke 2009; 40:2769–75
31. Sowade B, Sowade O, Mcks J, Franke W, Warnke H: The safety of treatment with recombinant human erythropoietin in clinical use: A review of controlled studies. Int J Mol Med 1998; 1:303–14
32. Woo S, Krzyzanski W, Jusko WJ: Pharmacokinetic and pharmacodynamic modeling of recombinant human erythropoietin after intravenous and subcutaneous administration in rats. J Pharmacol Exp Ther 2006; 319:1297–306
33. Fisher JW: Pharmacologic modulation of erythropoietin production. Annu Rev Pharmacol Toxicol 1988; 28:101–22
34. Fleming RE, Bacon BR: Orchestration of iron homeostasis. N Engl J Med 2005; 352:1741–4

35. Jacobs P, Finch CA: Iron for erythropoiesis. Blood 1971; 37:220–30
36. Paschos N, Lykissas MG, Beris AE: The role of erythropoietin as an inhibitor of tissue ischemia. Int J Biol Sci 2008; 4:161–8
37. Song YR, Lee T, You SJ, Chin HJ, Chae DW, Lim C, Park KH, Han S, Kim JH, Na KY: Prevention of acute kidney injury by erythropoietin in patients undergoing coronary artery bypass grafting: A pilot study. Am J Nephrol 2009; 30:253–60
38. Karkouti K, Wijeysundera DN, Yau TM, Callum JL, Cheng DC, Crowther M, Dupuis JY, Fremes SE, Kent B, Laflamme C, Lamy A, Legare JF, Mazer CD, McCluskey SA, Rubens FD, Sawchuk C, Beattie WS: Acute kidney injury after cardiac surgery: Focus on modifiable risk factors. Circulation 2009; 119:495–502
39. Corwin HL, Gettinger A, Pearl RG, Fink MP, Levy MM, Shapiro MJ, Corwin MJ, Colton T, EPO Critical Care Trials Group: Efficacy of recombinant human erythropoietin in critically ill patients: A randomized controlled trial. JAMA 2002; 288:2827–35
40. Kannel WB, Gordon T, Wolf PA, McNamara P: Hemoglobin and the risk of cerebral infarction: The Framingham Study. Stroke 1972; 3:409–20
41. Remuzzi G, Ingelfinger JR: Correction of anemia–payoffs and problems. N Engl J Med 2006; 355:2144–6

ANESTHESIOLOGY REFLECTIONS

Teter-ing into Advertising Anesthetic Services



Generated by developing a photograph on postcard-backed paper, "real photo postcards" (RPPCs) became a convenient way for hospitals, and perhaps doctor-anesthetists, to advertise their services in the early 1900s. Although dentists vacillated about whether advertising was professional, they generally advertised more readily than their physician colleagues. However, poorly remunerated physician-anesthetists might certainly have felt economic pressures to advertise their services. Inscribed with "Williamsport Hospital Dr.," this RPPC (*above*) features a dapper doctor-anesthetist (dentist or physician?) sporting a moustache and a bowtie. The anesthesia machine was manufactured by the Teter Manufacturing Company of Cleveland, Ohio. (Copyright © the American Society of Anesthesiologists, Inc. This image also appears in the *Anesthesiology Reflections* online collection available at www.anesthesiology.org.)

George S. Bause, M.D., M.P.H., Honorary Curator, ASA's Wood Library-Museum of Anesthesiology, Park Ridge, Illinois, and Clinical Associate Professor, Case Western Reserve University, Cleveland, Ohio. UJYC@aol.com.