Preoperative very short-term, high-dose erythropoietin administration diminishes blood transfusion rate in off-pump coronary artery bypass: A randomized blind controlled study

Luca Weltert, MD, Stefano D'Alessandro, MD, Saverio Nardella, MD, Fabiana Girola, MD, Alessandro Bellisario, MD, Daniele Maselli, MD, and Ruggero De Paulis, MD

Objective: Human recombinant erythropoietin has been used to obtain a rapid increase in red blood cells before surgery. Previously, the shortest preparatory interval has been 4 days, but at the European Hospital only 2.4 days on average separate hospitalization and surgery. We therefore proposed a randomized blind trial to test the efficacy of high-dose erythropoietin for very short-term administration.

Methods: All patients presenting with a diagnosis of isolated coronary vessel disease were randomized to either erythropoietin therapy or a control group. Patients with a creatinine level greater than 2 mg/dL or hemoglobin level greater than 14.5 g/dL were excluded. Hemoglobin values were collected preoperatively and on postoperative days 1 and 4. Blood loss and blood transfusion rate were recorded at the time of discharge.

Results: We enrolled 320 consecutive patients in the study. No significant difference was found in preoperative parameters, postoperative blood loss, or mean preoperative hemoglobin levels. On postoperative day 4, mean hemoglobin was 15.5% higher in the erythropoietin group (10.70 $\pm$ 0.72 g/dL vs 9.26 $\pm$ 0.71 g/dL; $P < .05$). This group required 0.33 units of blood per patient, whereas the controls required 0.76 units per patient (risk ratio 0.43, $P = .008$).

Conclusion: A significant reduction in transfusion rate and a significant increase in hemoglobin values were observed in the erythropoietin group. No adverse events related to erythropoietin administration were recorded. A very short preoperative erythropoietin administration seems to be a safe and easy method to reduce the need for blood transfusions. (J Thorac Cardiovasc Surg 2010;139:621-7)

The use of blood conservation techniques is important in cardiac surgery, because postoperative bleeding is common and allogenic blood transfusion carries the risk of transfusion reactions and infection. Specifically, in isolated coronary artery bypass grafting (CABG) the transfusion of allogenic blood increases the risk for postoperative atrial fibrillation, worsens health-related quality of life, and reduces long-term survival.[1-3] According to recent reports, more than one third of patients undergoing elective CABG still require allogenic blood, and approximately 20% of transfusions are associated with cardiac surgery. Erythropoietin with and without preoperative autologous blood donation is one way to minimize allogenic transfusion.[4] Erythropoietin is a 165 amino acid glycoprotein hormone with a molecular weight of approximately 30 kDa. It is synthesized primarily by the kidneys in adults and by the kidneys and liver in the fetus. The ratio between kidney and liver erythropoietin in adults is 9:1. Its primary role involves the prevention of programmed cell death (apoptosis) of erythrocyte precursors. Erythropoietin induces erythropoiesis by promoting the proliferation and differentiation of erythroid progenitor cells, the main target cell being the colony-forming unit erythroid.

In addition to erythropoietin's well-known effect on red blood cell mass in response to changes in tissue oxygenation, many investigations have shown that it also exerts a protective role against tissue ischemia. It is believed that this is achieved both directly by activating multiple biochemical mechanisms that provide anti-apoptotic, anti-oxidative, and anti-inflammatory responses to hypoxia/anoxia, and indirectly via its angiogenic potential by inducing a systematic oxygen supply to the ischemic tissue.[5]

Recombinant human erythropoietin (HRE) was developed in the mid-1980s and is commercially available in several forms. Erythropoietin combined with oral iron therapy is used to treat anemia (hemoglobin [Hb] < 13 g/dL) in renal failure, associated with chemotherapy or human immunodeficiency virus, and when given preoperatively, to reduce transfusion in a wide range of operations. Abundant evidence, including 4 meta-analyses,[6-9] exists to justify the preoperative administration of HRE to reduce preoperative anemia, especially in patients undergoing autologous blood donation[10-13] and in children.[14,15] Erythropoietin seems to

From the Cardiac Surgery Department, European Hospital, Rome, Italy.
Disclosures: None.
Received for publication April 30, 2009; revisions received Sept 9, 2009; accepted for publication Oct 4, 2009; available ahead of print Dec 30, 2009.
Address for reprints: Luca Weltert, MD, Cardiac Surgery Department, European Hospital, Rome, Italy (E-mail: lweltert@gmail.com).
0022-5223/$36.00

doi:10.1016/j.jtcvs.2009.10.012

Abbreviations and Acronyms
ANOVA = analysis of variance
CABG = coronary artery bypass grafting
Hb = hemoglobin
HRE = human erythropoietin

be safe and effective for the improvement of preoperative anemia. Preoperative interventions using HRE seem justified for elective patients with diminished blood volume because of the high risk of excessive blood transfusion in this subset. Still fewer objective data are available regarding the use of HRE to treat peri- and postoperative anemia. Because the onset of drug action is 4 to 6 days, it has been considered necessary to administer HRE a few days before the operation. There are some conditions in which the production of endogenous HRE is limited: beta-blocker therapy, cytokines stimulated by the inflammatory response associated with cardiopulmonary bypass, and perioperative renal ischemia. Likewise, careful perioperative management may improve tissue oxygen delivery and suppress endogenous HRE production despite postoperative anemia. All of these factors support the addition of preoperative (ie, a few days before surgery) administration of HRE to treat reduced red blood cell volume in selected patients.[16,17] So far, the shortest preparatory administration interval has been up to 4 days preoperatively.

At the European Hospital, an average of only 2.4 days separate hospitalization and surgery, and inpatient optimization procedures are pushing this limit even further. This situation is common in many high-volume centers, making any protocol requiring the patient to wait more than 3 days before operation unattractive and practically useless. We therefore proposed a randomized blind trial to test the efficacy of high-dose HRE in very short-term administration, a protocol that does not change the usual interval between admission and surgery. Should the advantages of HRE administration be present even with such a short interval, its use could be advisable as part of the routine strategy to minimize the use of allogenic blood transfusions.

MATERIALS AND METHODS

All patients presenting with a diagnosis of isolated coronary vessel disease at the European Hospital were considered for the study. Exclusion criteria were the presence of high Hb values (>14.5 g/dL, or hematocrit > 44%), confirmed renal impairment (creatinine > 2 mg/dL), or the need for on-pump revascularization. The decision to exclude the latter was made to avoid the confounding factor of extracorporeal circulation, which implies an increase in hemodilution and blood loss.

All patients' risk factors for ischemic heart disease (family history, the presence of diabetes, hypercholesterolemia, smoking, obesity, hypertension); factors included in the EuroSCORE analysis (age, gender, chronic pulmonary obstructive disease, the presence of extracardiac arteriopathy, neurologic dysfunction, previous cardiac surgery, serum creatinine, active endocarditis, critical preoperative state, unstable angina, left ventricle dysfunction, recent myocardial infarct, pulmonary hypertension, emergency conditions, postinfarct septal rupture); and biometric parameters (height, weight, and body surface area) were collected and stored in the database before the results of randomization were known. A custom simple application running in Windows XP (Microsoft Corp, Redmond, WA) was used to obtain randomization tables, and the next value of the table was kept secret until a suitable patient was enrolled. This study adheres to the CONSORT principles, and patients followed the CONSORT 2005 FlowChart.

Informed consent was then obtained, and all aspects of the operation, drug administration, and any other relevant matter were explained to the patient by one of the investigators. The study followed the Helsinki Declaration requirements for randomized case-control trials and was approved by the institutional review board of the European Hospital.

The patients randomized to the HRE group received 14,000 IU via subcutaneous administration 2 days before the operation, 14,000 IU on the next day, 8000 IU on the morning of the operation, 8000 IU 1 day after operation, and 8000 IU on postoperative day 2. The control group received no treatment. Despite known interactions of HRE with other medications (eg, beta-blockers), all standard therapies were maintained until the day of operation. The patients, nurses, and ward physician knew whether HRE was being administered or not, but the investigators did not, nor did they have any chance to influence the clinical decision as to whether or not to give allogenic blood, thus fulfilling the conditions for a single-blinded study.

The primary end point was the need for allogenic transfusion. The secondary end point was the Hb value on postoperative day 4. Ancillary objectives were the Hb trend from baseline to day 4 with and without HRE administration, and the cost-effectiveness of HRE versus the reduced need for transfusion.

Transfusion need was triggered by Hb levels less than 8.0 g/dL, and the same criteria were applied to both groups. Hb values were automatically collected by the central laboratory computer on the day of admission, on the day of surgery, and on postoperative day 4. The number of units transfused, the amount of blood loss, any kind of adverse reaction, and the patient's outcome were collected directly from the clinical records 2 weeks after discharge. All patients underwent outpatient follow-up approximately 45 days after surgery, at which time all adverse events were investigated.

All data were processed by SPSS version 16 (SPSS Inc, Chicago, Ill), including sample sizing, analysis of variance (ANOVA), and risk analysis. A preliminary power estimation analysis suggested that 160 patients per sample were needed to obtain a 90% power goal, considering an alpha error level of 5% and expecting the incidence of transfusion to decrease from the previously observed 30% to 15%.

The first step of analysis was to ascertain whether the randomization process had been effective in controlling as many known confounding factors as possible. ANOVA of the dependent variables ''HRE or control'' was performed (ANOVA and univariate ANOVA as needed, 95% confidence interval, P .05; full list of parameters and P values are shown in Table 1) on all preoperative data, namely, general cardiovascular risk parameters, EuroSCORE risk parameters, biometric parameters, and blood loss.

The second step was to verify whether the 2 groups really differed in terms of Hb value on day 4, transfusion rate, relative risk of undergoing allogenic blood transfusion, duration of hospital stay, and adverse events. Every comparison was tested with several statistical techniques (Student t test, univariate regression, Yates' continuity-corrected chi-square test as needed) as appropriate.

The general statistical aspect of the study was kept as simple as possible in the belief that even if sophisticated statistical techniques exist to control the influence of confounding factors, accurate planning remains the best tool.

RESULTS

Recruitment took place between October 1, 2007, and September 31, 2008, and 400 patients were assessed for