Impact of Erythropoietin on Allogenic Blood Exposure in Orthopedic Surgery

Jennifer E. Santoro, PharmD, Robert K. Eastlack, MD, James M. Mirocha, PhD, and William D. Bugbee, MD

Abstract

Joint reconstruction surgery is associated with significant blood loss, and patients often require perioperative transfusions. Recombinant human erythropoietin (epoetin) can be used in anemic patients scheduled for elective, noncardiac, nonvascular surgery to reduce the need for transfusions. In the study reported here, patients with a preoperative hemoglobin level of 10 to 13 g/dL were treated with epoetin. Our analysis showed that transfusions were given to 3 (8%) of the 38 patients who received epoetin before surgery and 20 (57%) of the 35 historical controls ($P<.001$) and that length of hospital stay did not differ significantly between the 2 groups. Our results provide further support for use of epoetin as an effective strategy for reducing exposure to allogenic blood in orthopedic surgery.

Joint reconstruction surgeries are associated with significant, predictable blood loss. Patients often become anemic and require perioperative blood transfusions. In a large study by Bierbaum and colleagues,[1] patients undergoing primary hip arthroplasty received a mean of 2 units of blood, and patients undergoing primary knee arthroplasty received a mean of 1.8 units. Several strategies have been developed to conserve blood and reduce exposure to allogenic blood—including preoperative autologous donation, hemodilution, intraoperative salvage, and postoperative reinfusion.[2,3] Among these, preoperative autologous donation is the most widely used in orthopedic surgery.[1]

Dr. Santoro is Clinical Pharmacy Manager, Pharmacy Management Department, CalOptima, Orange, California. Dr. Mirocha is Statistician, Cedars-Sinai Medical Center, Los Angeles, California.

Dr. Eastlack is Clinical Instructor, Department of Orthopaedic Surgery, University of California, San Diego, California.

Dr. Bugbee is Attending Physician, Scripps Clinic, La Jolla, California, and Associate Professor, Department of Orthopaedic Surgery, University of California, San Diego, California.

Requests for reprints: William D. Bugbee, MD, Division of Orthopaedic Surgery, Scripps Clinic, 10666 N Torrey Pines Rd, MS116, La Jolla, CA 92037 (e-mail, Bugbee.William@scrippshealth.org).

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Allogenic blood transfusions are associated with several potential infectious and noninfectious complications, including hepatitis, human immunodeficiency virus (HIV) infection, bacterial infections, hemolytic transfusion reactions, and allergic reactions.[1,4,5] Ten percent to 20% of patients who donate autologous blood before elective surgery still receive allogenic blood transfusions.[6] Therefore, exposure to allogenic blood is not completely eliminated. In addition, patients may not be eligible for autologous donation, either because of anemia or because of an inability to donate adequate amounts of autologous blood before surgery.[5,7] Autologous blood donation has several disadvantages. It is inconvenient and can increase the incidence of postoperative anemia.[8] There is also the (rare) potential for contamination of predonated blood or, through clerical errors, incorrect identification of the patient and/or unit before transfusion.[9]

"Allogenic blood transfusions are associated with several potential infectious and noninfectious complications."

Epoetin is approved for use in anemic patients scheduled for elective, noncardiac, nonvascular surgery. Several studies have shown that epoetin use can significantly reduce blood transfusions in orthopedic surgery.[6,8,10-14] Previous studies have demonstrated that baseline preoperative hemoglobin (Hb) level is a significant indicator of transfusion risk in surgery.[1,11,15,16] Epoetin has been found to be most effective in anemic patients with a preoperative Hb level of 10 to 13 g/dL.[11,15,16] Epoetin works by increasing preoperative Hb level in anemic patients and promoting postoperative Hb recovery.[8,10,13] In clinical studies, epoetin was well tolerated and had few associated side effects.[6,8,10-13]

A low postoperative Hb level can extend length of hospital stay for patients undergoing joint arthroplasty. Bierbaum and colleagues[1] compared hospitalization duration in 3 patient groups—those who received a transfusion of allogenic blood, those who received autologous blood, and those who were not transfused. The shortest hospital stay (~5 days) was seen in the group that did not receive a transfusion.

In the current retrospective study, we evaluated the impact of using epoetin in anemic patients in an ortho-

Table I. Patient Background Characteristics*

Characteristic	Epoetin (n = 38)	Control (n = 35)	*P*
Age (y)	62.3±17.3	63.8±13.3	.684
Sex			
Female	34 (89)	30 (86)	.729
Male	4 (11)	5 (14)	
Weight (kg)	71.8±17.3	79.5±21.1	.095
Baseline hemoglobin (g/dL)	11.9±1.1	12.1±0.9	.399
Hypertension	14 (37)	20 (57)	.103
Other cardiovascular disease	3 (8)	5 (14)	.245

*Variables expressed as mean ± SD or n (%).

pedic surgeon's practice. Historical controls were used to obtain comparison data from a time before epoetin was widely used in this surgeon's practice for anemic patients undergoing primary hip or knee arthroplasty. The primary outcome measure was exposure to allogenic blood, measured by number of patients transfused. In addition, length of stay was compared between the 2 groups.

Materials and Methods

Study Design and Patients

A retrospective, historical-control comparative study design was used. The study population consisted of patients who underwent primary total hip arthroplasty (THA) or primary total knee arthroplasty (TKA) performed by an orthopedic surgeon at the University of California, San Diego Medical Center. The medical center's institutional review board approved this study.

All 73 patients in this study were 18 years old or older, underwent THA or TKA between March 1998 and August 2000, and had a preoperative Hb level >10 g/dL and ≤13 g/dL. Patients with uncontrolled hypertension as noted in the medical record were excluded from the study (uncontrolled hypertension is a contraindication for use of epoetin).

The treatment group consisted of 38 patients who received epoetin before surgery. Epoetin (40,000 units, or ~600 U/kg) was given by subcutaneous injection 21, 14, and 7 days before surgery and on the day of surgery. This is one of the FDA-approved treatment regimens for epoetin in anemic patients scheduled for elective, noncardiac, nonvascular surgery. Patients eligible for epoetin therapy had a preoperative Hb level >10 g/dL and ≤13 g/dL. Patients took iron supplements while receiving epoetin therapy. For these patients, surgery was performed between April 1999 and August 2000. In February 1999, the surgeon had begun using epoetin in several of his patients on the basis of preoperative Hb level, estimated surgical blood loss, and the surgeon's clinical judgment. In September 1999, he began using epoetin in all his patients who had a preoperative Hb level >10 and ≤13 g/dL and who were undergoing joint reconstruction surgery associated with significant estimated blood loss.

The historical-control group was selected by screening all patients who had undergone orthopedic surgery before September 1999. Patients with an Hb level >10 and ≤13 g/dL were selected from those who had surgery performed between March 1998 and August 1999. The 35 patients who met these criteria and whose medical records were complete during time of admission for orthopedic surgery were included in the study. These patients served as historical controls. None of these patients received epoetin before surgery.

Baseline Hb level was either the initial preoperative Hb level before initiation of epoetin therapy (treatment group) or the baseline Hb level as measured during preoperative laboratory work (control group). Other preoperative data collected were age, sex, weight, surgery date, comorbid conditions (other than arthritis), and relevant chronic medications. Comorbid conditions included diabetes, coronary artery disease, hypertension, systemic lupus erythematosus, and other cardiovascular disease (atrial fibrillation, congestive heart failure, and aortic stenosis; grouped because of low incidence). Relevant chronic medications included iron, aspirin, warfarin, and nonsteroidal anti-inflammatory drugs. Comorbidities and certain chronic medications can increase the need for transfusion and contribute to longer hospitalization.[3]

Intraoperative data collected included surgery type, estimated blood loss, and number of units transfused. Estimated intraoperative blood loss was determined from the anesthesia record, the dictated operation summary, or the postoperative progress note in the medical record. Postoperative data collected included Hb level, number of transfusions, and hospitalization duration.

Decisions to transfuse were based on intraoperative blood loss, Hb and hematocrit levels, and the surgeon's clinical assessment. The same surgeon operated on all the patients included in this study, and criteria and judgment were consistent over the course of the study. All patients received deep vein thrombosis prophylaxis with either low-molecular-weight heparin or warfarin. Data were collected from the University of California, San Diego computerized patient database and from patients' medical records.

Statistical Tests

Summary statistics for continuous variables are expressed as means (SDs), and summary statistics for categorical variables are expressed as numbers (percentages).

Table II. Surgical Procedure and Intraoperative Blood Loss

Variable	Epoetin (n = 38)	Control (n = 35)	*P*
Surgical site			
Hip	26 (68)	24 (69)	.327
Knee	12 (32)	11 (31)	
Intraoperative blood loss (mL)			
Hip + knee	334±218 (n = 37)†	411±214 (n = 34)†	.139
Hip	438±194 (n = 25)†	462±193 (n = 26)†	.650
Knee	144±97 (n = 12)†	244±201 (n = 8)†	.221

*Variables expressed as mean ± SD or n (%). †Data not available for all patients.

Table III. Transfusion Requirements, Postoperative Hemoglobin, Length of Hospital Stay*

Variable	Epoetin (n = 38)	Control (n = 35)	*P*
No. transfused patients	3 (8)	20 (57)	<.001
No. units per transfused patient	1.7±0.6	2.1±0.9	.656
Postoperative hemoglobin (g/dL)	10.9±1.6	9.4±1.2	<.001
No. days hospitalized	5.3±1.1	5.7±1.4	.135

*Variables expressed as mean ± SD or n (%).

Treatment–control differences on continuous variables with approximately normal distributions were assessed with the Student *t* test using the Satterthwaite adjustment when there was evidence against homogeneity of variance; when there was evidence of nonnormality, treatment–control differences were assessed with the Wilcoxon 2-sample test. Treatment–control comparisons of categorical variables were assessed with Fisher's exact test. *P*s are given for all significance tests. Calculations were performed with SAS Version 8.2 (SAS Institute, Cary, NC).

Results

Patient Background Characteristics

In this study, 73 patients were evaluated—38 who received epoetin before surgery and 35 historical controls. Table I summarizes these groups' background characteristics. Age and sex were similar for the groups. Mean age was 63 years (SD, 15 years; range, 24-86 years). Patients were predominantly female (89% of epoetin group, 86% of control group). The groups were also similar in weight. In addition, frequency of comorbid conditions and use of relevant medications were similar. Hypertension was the most common comorbid condition, occurring in 37% of epoetin patients and 57% of controls ($P = .103$). "Other cardiovascular disease" (previously defined) was found in 8% of epoetin patients and 14% of controls ($P = .245$). The groups were similar in mean baseline Hb level, which was 12.0 g/dL (SD, 1.0 g/dL) for all patients.

Table II summarizes surgery types (primary THA was most common) and mean amounts of intraoperative blood loss (lower for TKA than THA).

Transfusion Data

Transfusions were given to 8% (3/38) of epoetin patients and 57% (20/35) of controls—a significant difference ($P<.001$). Table III summarizes both groups' transfusion requirements. Transfused epoetin patients received a mean of 1.7 units of blood (SD, 0.6 U), and transfused controls received a mean of 2.1 units (SD, 0.9 U); the difference is not statistically significant ($P = .656$). Mean postoperative Hb level was significantly ($P<.001$) higher for epoetin patients (10.9 g/dL; SD, 1.6 g/dL) than for controls (9.4 g/dL; SD, 1.2 g/dL).

Length of Hospital Stay

Length of stay did not differ ($P = .135$) between epoetin patients (mean, 5.3 days; SD, 1.1 days) and controls (mean, 5.7 days; SD, 1.4 days). Median length of stay was 5 days for both groups.

Units Transfused and Length of Stay

For those patients receiving a transfusion (n = 23), longer hospitalization was associated with more units being transfused ($r = 0.536$, $P = .009$).

Safety Data

Safety was not evaluated as an outcome measure, but we note that there were no adverse events reported in the medical records of any patients.

Discussion

The objective of this study was to evaluate the success of preoperative use of epoetin in patients at heightened (but not absolute) risk for postoperative transfusion.

Preoperative autologous donation was not an option for these patients because of their relative anemia (Hb, 10-13 mg/dL). In comparison with historical controls, patients who received epoetin before surgery showed a considerable decrease in the rate of allogenic blood transfusions after total joint arthroplasty (TJA). Rates of postoperative allogenic blood transfusion dropped from 57% to 8% with use of epoetin before primary THA or TKA.

The need for blood transfusion with TJA is a concern of orthopedic surgeons. A substantial drop in Hb level or hematocrit level can expose the patient to increased hemodynamic and cardiopulmonary risks. Postoperative blood transfusions are given, but research has shown that they do not adequately raise Hb to preoperative levels.[17] More important, blood transfusions carry substantial risks for infection transmission and transfusion reactions. Hepatitis and HIV infection are 2 of the more common infection concerns, but there are many others.[1,4,5] Transfusion reactions, which may be substantial, can occur through exposure to major or minor blood proteins, or through clerical error.[4,5,9] In addition, religious concerns may obviate use of blood transfusions altogether.

Preoperative autologous donation has been used to address some concerns about allogenic blood transfusions—including infection risk—but it does not eliminate the possibility of other deleterious reactions or clerical error.[9] Patients with tenuous cardiopulmonary conditions may still have significant difficulties with volume changes associated with transfusion of packed red blood cells. There is evidence that autologous donation reduces the need for allogenic blood transfusion after TKA. However, because autologous donation lowers preoperative Hb levels, it can increase the risk for required postoperative blood transfusion.[1,3,6] Finally, surgery postponement, which is not uncommon, may result in wasted autologous blood products (they must be used in a timely manner).

Many TJA patients are not good candidates for preoperative autologous donation.[5,7] A low baseline Hb level (<13 mg/dL) precludes autologous blood donation while substantially increasing the risk for postoperative transfusion. Previous investigators have found that preoperative Hb level is the most significant predictor of transfusion risk with THA or TKA.[1,11,15,16]

Given the varied risk profiles for postoperative blood transfusion, surgeons must develop relevant clinical algorithms to address patients' needs before surgery is performed. According to a study by Salido and colleagues,[17] patients with a preoperative Hb level <13 mg/dL had 4 times the risk for required blood transfusion over patients with a level of 13 to 15 mg/dL. Patients with a level >15 mg/dL seldom required postoperative transfusions. In contrast, patients with a level <10 mg/dL almost universally require allogenic blood transfusions after surgery. Analyzing patients' preoperative risks and other relevant clinical conditions allows surgeons to intervene with appropriate therapeutic modalities, such as epoetin. In the current study, we analyzed these risks and conditions at initial evaluation, typically 2 to 4 months before surgery. It was at that time that we measured Hb levels to identify patients with anemia.

This study clearly demonstrates a marked reduction in need for blood transfusion with use of epoetin before primary THA or TKA. Our results support previous findings that epoetin use is associated with reduced transfusion rates.[6,8,10-15] Such an effect has been theorized to result from increased preoperative Hb levels and from a more rapid rate of recovery over the postoperative period.[8,10,13]

Transfusion rates and epoetin use did not correlate with shorter hospital stays in the current study. However, statistical power for this parameter may have been limited by the small number of epoetin patients matched with historical controls. Bierbaum and colleagues[1] demonstrated an association between allogenic blood transfusions and longer hospital stays in a study of 9482 orthopedic surgery patients. Mean hospitalization duration was 1 day longer for those who received allogenic blood (6.6 days) than for patients who received autologous blood (5.6 days) or for patients who did not receive a transfusion (5.4 days).

Variability in clinicians' thresholds for transfusing blood products can lead to considerable skewing of transfusion rates in certain study designs. A standard algorithm applied by a single clinician allows for more uniform use of transfusions and generates less variability. In our study, a single orthopedic surgeon made all the decisions regarding blood product transfusions and applied clinical judgment in a consistent manner. Each transfusion decision was based on the patient's clinical and laboratory data and risk factors for complications of anemia.

Despite the retrospective nature of this study, the closely matched historical control group was almost contemporary with the treatment group. Early use of epoetin in the surgeon's practice empirically demonstrates a significant impact on transfusion requirements, so prospective evaluation was abandoned in favor of the retrospective design. The large difference in transfusion rates between treatment and control groups supports use of retrospective analysis.

Many patients who undergo primary hip or knee arthroplasty are anemic before surgery. Preoperative autologous donation, however, has substantial disadvantages and is sometimes contraindicated entirely. In a small subgroup of these patients, anemia is significant, and postoperative allogenic transfusion may be unavoidable. However, most patients in this subgroup have relative anemia and may benefit greatly from preoperative intervention. Appropriate use of preoperative epoetin can play a major role in reducing patients' need for the blood transfusions associated with primary joint arthroplasty.

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