The Open Orthopaedics Journal, 2013, *7*, 47-50

Should We Use Preoperative Epoetin-α in the Mildly Anemic Patient Undergoing Simultaneous Total Knee Arthroplasty?

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Abstract: Simultaneous knee arthroplasty is associated with significant blood loss. To prevent transfusion, three preoperative doses of epoetin-α were offered to mildly anemic simultaneous knee arthroplasty patients. A retrospective review, using ICD-9 codes, identified twenty patients from 2007-2009. Epoetin-α increased hemoglobin levels preoperatively (12.6 to 13.9, $p<0.01$). Twenty patients who did not receive epoetin-α were matched to study patients. Study patients were transfused less (55% *vs* 95%, $p=0.012$) and had similar inpatient length of stay. The average blood loss without transfusion was 4.6g/dL. The mildly anemic patient is at high-risk for packed red cell transfusion during simultaneous knee arthroplasty. Three preoperative doses of epoetin-α in the mildly anemic patient decreased total transfusions; however, it did not affect inpatient length of stay.

Keywords: Single stage bilateral total knee arthroplasty, simultaneous total knee arthroplasty, epoetin-α, tranexamic acid, degenerative joint disease, pain, anemia.

INTRODUCTION

Substantial blood loss occurs during elective knee arthroplasty [1, 2]. Simultaneous bilateral total knee replacement has an even higher blood loss and, consequently, these patients are more likely to receive packed red cells [3]. However, blood transfusion is associated with morbidity. Furthermore, patients may refuse transfusion due to religious beliefs [4]. Therefore preoperative interventions are important to prevent transfusion [5-8].

Approximately twelve percent of patients (≥65yoa) are mildly anemic [9]. The mildly anemic patient has a four-fold and fifteen-fold transfusion rate increase over patients with preoperative counts of 13.0-15.0g/dl and >15g/dl, respectively [10, 11]. Epoetin-α delivered as three preoperative doses is believed to increase preoperative hemoglobin counts, and has been shown to reduce transfusion and decrease inpatient length of stay in the mildly anemic patient undergoing a revision hip and/or knee arthroplasty [12, 13]. Furthermore, it is unknown whether preoperative epoetin-α is a useful intervention in the mildly anemic simultaneous total knee arthroplasty patient.

Tranexamic acid is another viable option to prevent allogeneic transfusion [14]. It is a synthetic serine protease analog that reversibly inhibits fibrinolysis – a major cause of postoperative bleeding. It blocks lysine residues that bind plasmin and plasminogen activator molecules. The drug has similar applications in cardiac, urologic, and gynecologic surgeries as well as liver transplantation. Aprotinin and Aminocaproic acid have also been suggested. Aprotinin (derived from bovine lung) inhibits the serine protease during the final stage of fibrinolysis; however, allergies, thrombosis, nephrotoxicity, and spongiform encephalopathy have led to its decreased international use [15]. Furthermore, Aminocaproic acid is less effective, more expensive, and less efficacious than tranexamic acid [16].

This is the first study, to the knowledge of these authors, to assess pre-operative epoetin-α injections on the mildly anemic patient (10-13g/dL) undergoing simultaneous total knee arthroplasty. The purpose is to evaluate the preoperative change in hemoglobin, quantify overall blood loss, and to compare the percent of patients transfused with blood. The hypotheses are that three preoperative doses of epoetin-α will decrease transfusions and reduce inpatient length of stay.

METHODS

Following Institutional Review Board (IRB) approval, we performed this retrospective study. Between April 2007 and August 2009, a retrospective review using ICD-9 coding, identified 95 patients who underwent a simultaneous bilateral total knee arthroplasty. Fifty patients were mildly anemic (10-13g/dL), preoperatively. Twenty of these mildly anemic patients received three preoperative doses of epoetin-α (21, 14, and 7 days prior to surgery). Patient-matching occurred by procedure, gender, BMI, ASA score, and age. Patient's with pre-operative Hgb values less than 10 g/dL or

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1874-3250/13

greater than 13g/dL, dual stage bilateral knee arthroplasty, a history of prior deep venous thrombosis or a pulmonary embolus, patients who received a postoperative drain, and patients with hematological diseases, cancer, or coagulation disorders were excluded. Mild anemia was defined by a Hgb level at or below 13g/dL and at or above 10g/dL [10, 11].

Prior to epoetin-α administration, all mildly anemic patients were appropriately counseled by an expert about the risks and benefits of preoperative anemia treatment. Anemic patients were considered for three weekly subcutaneous doses of 40,000 U of epoetin-α. All injections were combined with supplemental oral iron. All patients were offered oral multi-vitamins, vitamin B12, folic acid, and iron.

The preoperative work-up, surgical technique, anesthesia, and postoperative management of patients in both groups were similar. All surgeries were completed under combined spinal-epidural anesthesia, with tourniquet control. A straight medial para-patellar approach was used. All knee arthroplasties were cemented. Neither cell saver nor drains were used. Through 4-weeks postoperative, proper anticoagulation (either oral warfarin or subcutaneous enoxaparin) was administered. The target INR was 2.0-2.5. The clinical triggers for blood transfusion during or after the procedure were determined based on peri- and postoperative hemoglobin levels, the ASA score (American Society of Anesthesiologists) of the patient, and/or clinical symptoms consistent with an anemia.

Twenty patients (50%) received epoetin-α. There were no differences between groups based on mean age (66 *vs* 64 years), BMI (30.7 *vs* 30.8 kg/m^2), preoperative INR (0.97 *vs* 1.01), or platelet count (268,737 *vs* 265,750 per mm^3) (p>0.05). The distribution of patients according to ASA score was similar (p=0.65) (Table **1**).

Table 1. Patient Demographics

Characteristic	Epoetin-α	Control	P-Value
Age	66	64	P=0.80
BMI	30.7	30.8	P=0.90
Preoperative INR	0.97	1.01	P=0.90
Platelet count	268,737	265,750	P=0.70
ASA score	2.32	2.2	P=0.65

An a priori sample size was calculated for a student's t-test evaluation. The anticipated effect size was 0.85, desired statistical power level was 0.8, and probability level was 0.05. Therefore, the minimum sample size per group to test the hypothesis was 18. A chi-square test for the proportions of cases receiving blood, and Student's *t*-test and Chi-square were used for comparing the continuous and categorical variables, respectively. For the statistical analysis, version 18 of PASW® Statistics (SPSS Inc., an IBM Company Headquarters, Chicago, Illinois) was used. A p<0.05 was considered statistically significant.

RESULTS

The mean Hgb level at time of surgery was higher in patients who received preoperative epoetin-α (13.9 *vs* 12.44 g/dL) (p=0.0001). Epoetin-α increased the preoperative hemoglobin level from 12.6 to 13.9 (P=0.0001). The average duration of surgery was similar (103 *vs* 109 minutes) (p=0.18). The intervention cohort had a blood loss from pre- to immediately postop of 4.6g/dL. There was no difference in the hemoglobin level at time of transfusion (8.2 *vs* 8.5) (p=0.31). At discharge, there was no difference in Hgb level (8.95 *vs* 8.90 g/dL) (p=0.83). Patients receiving epoetin-α were transfused less (55% (11 of 20) *vs* 95% (18 of 20)) (p=0.012). There were no difference in number of units transfused (1.45 *vs* 1.3units) (P=0.60)). Thirty-six percent of transfusions occurred on postoperative day 1; thirty-six percent on postoperative day 2; twenty-seven percent occurred on postoperative day 3. There was no difference in day of transfusion. There was no difference in length of hospital stay (3.26 *vs* 3.25days) (p=0.95) (Table **2**).

Table 2. Results. Note that Epoetin-α Increased hgb Counts Preoperatively and Decreased Transfusions

Characteristic	Epoetin-α	Control	P-Value
Hb at initial visit (g/dL)	12.6 to 13.9	NA	P=0.0001
Hb on day of surgery (g/dL)	13.9	12.44	P=0.0001
Hb at time of transfusion (g/dL)	8.2	8.46	P=0.31
Transfusion (%)	55%	95%	P=0.012
Length of Stay (days)	3.25	3.26	P=0.83
Hb on discharge (g/dL)	8.95	8.9	P=0.83
Duration of surgery (mins)	103	109	P=0.18

One of the patients in the control group developed cellulitis four days after surgery which was completely resolved with antibiotic treatment. Another patient in this group developed a myocardial infarction five days following knee replacement. One patient in the epoetin-α group (65 year old male) passed away seven months after surgery due to cardiac arrest. No other minor or major complication, either local or systemic, was recorded in either cohort.

DISCUSSION

The blood loss during a simultaneous bilateral total knee arthroplasty surgery is substantial, and most mildly anemic (Hgb 10-13) patients will require transfusion. Three preoperative subcutaneous injections of 40,000 U of epoetin-α were successful at increasing preoperative blood counts, and decreasing transfusion.

De Andrade *et al.* compared epoetin-α to a placebo in a primary total knee arthroplasty double-blind study and noted that patients with mild anemia (10-13g/dl) who received epoetin-α were transfused less [17]. Stowell CP *et al.* found that weekly epoetin-α doses of 40,000 units raised hemoglobin levels from 12.3 g/dL to 13.8 g/dL, preoperatively. Their patients maintained higher levels peri- and postop compared to those receiving autologous blood [18]. Epoetin-α increased hemoglobin levels in this study (12.6 to 13.9g/dl) resulting in a 40% decrease in the overall effect on transfusion practice. However, there was no effect on decreasing inpatient length of stay as demonstrated previously [12, 13].

All cases were performed under tourniquet control, which along with postoperative fibrinolysis can increase blood loss after arthroplasty [19-21]. Epoetin-α is believed to transiently increase as well as improve platelet function, which theoretically decreases total blood loss [22]. This study did not calculate a hidden blood loss, but it did note that total blood losses during simultaneous knee arthroplasty were higher than primary knee, revision knee, and/or revision hip surgeries [23]. The change in hemoglobin from pre- to postop in our intervention cohort was 4.6 g/dL without re-infusion; such a change appears comparatively higher than that recorded by Sehat KR *et al.* who noted that a primary knee arthroplasty without re-infusion had a change of 3.3 g/dL and 2.8 g/dL after re-infusion. Interestingly, the change in blood count may be hidden in soft tissue and the joint of an arthroplasty patient [23] – which was demonstrated in two radio-labeled RBC studies that showed peri-operative blood loss into the soft tissue compartments [24, 25]. Although this study suggests that mildly anemic patients benefit from three preoperative doses of epoetin-α, the substantial blood loss during this procedure suggests that the goal of 'bloodless medicine' may require an additional intervention.

To achieve 'bloodless medicine', augmenting epoetin-α use in this population with tranexamic acid may be an additional option. Tranexamic has been shown to prevent fibrinolysis, and Ortega-Andreu M *et al.* showed that two doses, given intraoperatively, demonstrated a decrease in postoperative blood loss and transfusion practice in a multimodal protocol during primary total knee arthroplasty [14]. Future study to evaluate the combination of these two treatment modalities may demonstrate decreased blood loss and transfusion allowing earlier participation in physical therapy and/or achieving milestones sooner [2, 17, 26-28] in the mildly anemic simultaneous total knee arthroplasty population.

Epoetin-α has been shown, in selected patient groups, to decrease total cost during primary knee arthroplasty [29, 30]. One study showed it increased direct cost per patient when compared to a re-transfusion system [31]; however, the indirect costs were not analyzed and the authors noted that true cost-effectiveness could not be determined. Our experience using epoetin-α has been safe and effective at increasing cell counts. Furthermore, the weekly dosing regimen appears more patient friendly and cost effective to reported alternatives [32]. Furthermore, the elevated preoperative hemoglobin level may improve short-term outcomes [26].

Epoetin-α is thought to also have anti-apoptotic activity that can protect cells from hypoxic and ischemic events [33-35]. Interestingly, cancer and chronic renal failure patients were noted to have an increased thrombosis rate and death [36-38]. This study had one unrelated cardiovascular incident. A myocardial event occurred seven months postoperative unrelated to drug use. Furthermore, all patients received the same immediate postoperative treatment course that consisted of anti-thromboprophylaxis, early ambulation, and physical therapy.

No retrospective study design is without limitation. To increase similarity between patient groups, patient-matching occurred based on age, gender, procedure, BMI, and American Society of Anesthesiology (ASA) scores. Each cohort was a consecutive series of mildly anemic (10-13 g/dl) patients. Ninety percent of patients underwent spinal anesthesia in both cohorts, which is associated with decreased blood loss in the hypotensive patient [39]. The study group reported increased pre-operative iron, folic acid, vitamin B12, and multivitamin use. Cases were performed by two senior surgeons who use identical indications for transfusion based on peri- and postoperative hemoglobin levels, ASA score (American Society of Anesthesiologists), and/or symptomatic anemia. Lastly, no difference in ASA scores or hemoglobin counts at the time of transfusion between cohorts were noted.

In conclusion, the mildly anemic patient is at high-risk for transfusion during simultaneous bilateral total knee arthroplasty. A three week dosing regimen of 40,000 U of epoetin-α increases the preoperative blood count and decreases transfusion. To achieve the goal of preventing transfusion in the mildly anemic simultaneous total knee arthroplasty patient, additional interventions are likely necessary to not only achieve 'bloodless medicine', but also increase participation in physical therapy, achieve milestones sooner, and decrease overall inpatient length of stay.

CONFLICT OF INTEREST

The authors confirm that this article content has no conflict of interest.

ACKNOWLEDGEMENTS

Declared none.

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Received: November 22, 2012 Revised: January 17, 2013 Accepted: January 23, 2013