

PREOPERATIVE USE OF RECOMBINANT HUMAN ERYTHROPOIETIN BEFORE TOTAL JOINT ARTHROPLASTY

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Background: Previous reports have suggested that the use of recombinant human erythropoietin is effective for decreasing the need for perioperative allogeneic blood transfusion. The purpose of this study was to evaluate the efficacy of erythropoietin in combination with, and compared with, preoperative autologous donation for reducing allogeneic blood requirements for total joint arthroplasty.

Methods: Two hundred and forty patients undergoing primary and revision total hip or knee arthroplasty were enrolled into three groups with different treatment regimens: (1) erythropoietin and preoperative autologous donation (Group 1), (2) erythropoietin alone (Group 2), and (3) preoperative autologous donation alone (Group 3). Patients were evaluated with regard to requirements for allogeneic transfusion, change from the baseline to the lowest postoperative hemoglobin value, postoperative complications, and adverse reactions.

Results: The rate of allogeneic transfusion was 11% in Group 1 (erythropoietin and preoperative autologous donation) compared with 28% in Group 2 (erythropoietin alone) and 33% in Group 3 (preoperative autologous donation alone). Within Group 1, patients who had a unilateral primary arthroplasty had an allogeneic transfusion rate of 4% and those who had a bilateral or revision arthroplasty had an allogeneic transfusion rate of 17%. In Groups 2 and 3, the allogeneic transfusion rates were 14% and 15%, respectively, for the patients who had a unilateral primary arthroplasty and 35% and 47%, respectively, for those who had a bilateral or revision arthroplasty.

Conclusions: Preoperative use of erythropoietin in conjunction with preoperative autologous donation reduces the need for allogeneic blood transfusion associated with total joint arthroplasty more effectively than does either erythropoietin or preoperative autologous donation alone.

Level of Evidence: Therapeutic study, Level II-1 (prospective cohort study). See Instructions to Authors for a complete description of levels of evidence.

Blood loss associated with total joint arthroplasty can be substantial. Lotke et al.¹ estimated that 1500 mL of blood is lost in association with a unilateral total knee arthroplasty. Historically, this blood has been replaced, when needed, with banked blood, which may be a limited resource in some centers. Concerns regarding infectious complications as well as transfusion reactions have led to the development of preoperative autologous donation programs. However, preoperative autologous donation has been associated with scheduling difficulties, a limited shelf life for the blood, perioperative anemia², potential clerical error³, and bacterial contamination^{4,5}. Although it is commonly perceived that blood from a designated donor is superior to allogeneic blood, blood from a designated donor may actually be associated with greater risks of infection

than allogeneic blood⁶⁻⁸. Recent techniques that have been employed to optimize blood conservation include use of pharmacologic agents^{9,18}, hemodilution^{19,20}, and perioperative blood salvage^{18,21-25}. The most extensively evaluated pharmacologic agent has been recombinant human erythropoietin⁹⁻¹⁷. Erythropoietin is a glycoprotein excreted by the kidney, and its function is to stimulate production of red blood cells. Various studies have shown its efficacy in the treatment of renal, chemotherapy, and retroviral-related anemia²⁴. Recent randomized studies have shown that the preoperative use of erythropoietin reduces the need for allogeneic blood transfusions⁹⁻¹⁷. When combined with preadmission donation, erythropoietin increases the amount of blood that is predonated, while reducing the risk of perioperative anemia²⁵. Although authors of previous studies have included total joint arthroplasties, many failed to include large numbers of revision and bilateral arthroplasties. The purpose of the present study was to evaluate the efficacy of erythropoietin, combined with and in comparison with preoperative autolo-



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gous donation, for reducing allogeneic blood requirements in total joint arthroplasty.

Materials and Methods

A prospective, randomized, open-label, parallel-group study was conducted at a single institution. Enrollment criteria included an age of more than twenty-one years, a patient scheduled to undergo total joint arthroplasty, an initial hemoglobin level of ≤ 140 g/L, and a willingness to participate in a preoperative autologous donation program. Women who participated had to be postmenopausal, sterile, or taking oral contraceptives. Pregnant women were excluded. Other exclusion criteria included a clinically relevant uncontrolled systemic disease or abnormal laboratory values, primary hematological disease, a seizure disorder, uncontrolled hypertension, recent gastrointestinal or intracranial hemorrhage, and iron deficiency. All patients provided informed consent and were randomly assigned to one of three treatment groups. The study was approved by the institutional review board.

The first 240 patients who presented for total joint arthroplasty in 2000 and 2001 and who agreed to participate in the current study were randomly assigned to one of three groups. Patients in Group 1 received erythropoietin and underwent preoperative autologous donation, patients in Group 2 received erythropoietin alone, and patients in Group 3 underwent preoperative autologous donation alone. All procedures were performed by the senior authors (D.G.N. and R.E.B. Jr.). Patients receiving erythropoietin (Groups 1 and 2) were given 600 IU/kg of the drug subcutaneously in a four-dose regimen, twenty-one days, fourteen days, seven days, and one day prior to the surgery. Patients receiving erythropoietin were also given a single dose of 100 mg of intravenous iron dextran at the time of the initial erythropoietin dose, followed by oral supplementation with 325 mg of iron sulfate twice daily. Patients undergoing preoperative autologous donation were requested to donate one unit of blood for a primary unilateral arthroplasty and two units for a bilateral or revision arthroplasty. All patients undergoing preoperative autologous donation received oral supplementation with 325 mg of iron sulfate three times daily.

Age, sex, height, weight, type of arthritis, medical comorbidities, and type of joint arthroplasty were recorded for each patient. Hemoglobin levels were measured at baseline (screening), immediately preoperatively, and daily postoperatively prior to discharge. The lowest postoperative hemoglobin level and pretransfusion hemoglobin level were noted for comparison.

Transfusion data were collected for all patients. The indications for perioperative blood transfusion included a hemoglobin level of ≤ 80 g/L and/or persistent tachycardia or hypotension requiring administration of large volumes of crystalloid. Clinical symptoms was an additional criterion for allogeneic blood transfusion in the postoperative period.

All patients received spinal anesthesia during the operative procedure and epidural anesthesia for postoperative pain management. Adjusted-dose warfarin was used for prophylaxis

against deep venous thrombosis, with an international normalized ratio of approximately 2 as the goal. All patients treated with unilateral total knee arthroplasty or unilateral total hip arthroplasty had placement of standard Hemovac drains, which were removed forty-eight hours postoperatively. Intraoperative blood salvage (with a cell-saver device) was used during revision total hip arthroplasty. Reinfusion drains were used in the revision total knee arthroplasties and bilateral total knee and total hip arthroplasties. The reinfusion drains (for cell salvage) were used for capture during the contralateral procedure and in the immediate postoperative period in the recovery room and then were converted to standard Hemovac drains. All drains were removed forty-eight hours following the arthroplasty. Adverse reactions and complications were recorded.

The primary efficacy variables were the percentage of patients in each group requiring allogeneic blood and the mean number of units given to each patient who received a transfusion. The secondary efficacy variable was a change in hematological parameters. Statistical analyses were performed with a two-way analysis of variance. Significance was placed at the 0.05 level of probability.

During the study period, 396 patients presented for a total hip or knee arthroplasty and 65% (257) of them met the criterion of a baseline hemoglobin level of ≤ 140 g/L. Seventeen patients declined to be in the study. Of the remaining patients, eighty received erythropoietin and underwent preoperative autologous donation (Group 1), eighty received erythropoietin alone (Group 2), and eighty underwent preoperative autologous donation alone (Group 3). One hundred and forty-four (60%) of the patients were women, and ninety-six were men.

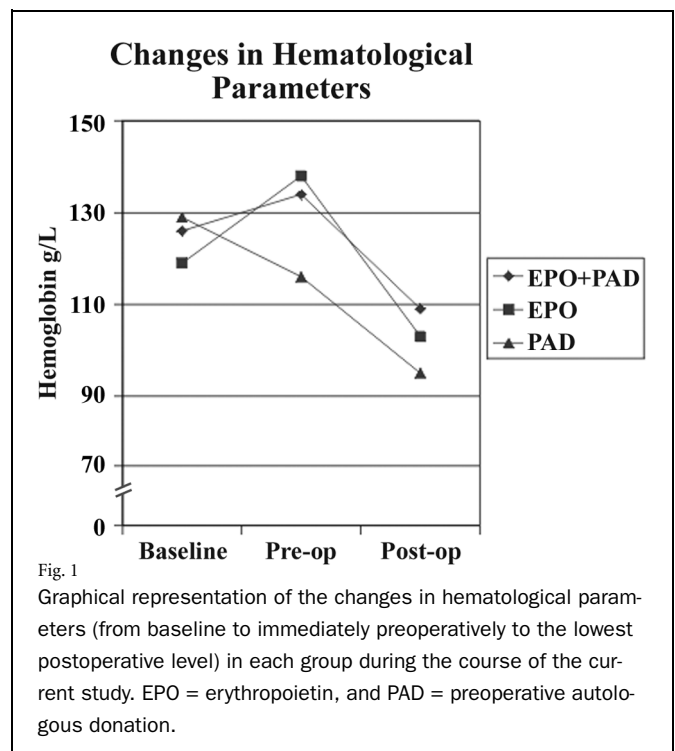


TABLE I Patient Demographics*

	Group 1	Group 2	Group 3
No. of patients	80	80	80
Mean age (range) (yr)	61 (55-81)	65 (48-79)	63 (50-80)
Male/female (no.)	35/45	27/53	34/46
Mean weight (range) (kg)	79 (50-132)	74 (52-129)	77 (51-143)
Mean height (range) (cm)	168 (140-188)	165 (142-192)	163 (144-190)
Osteoarthritis (no.)	73	70	77
Inflammatory arthritis (no.)	7	10	3
Mean baseline hemoglobin level (range) (g/L)	126 (93-140)	119 (83-140)	129 (100-139)
Comorbidities (no.)			
Cardiovascular	25	36	28
Renal	4	5	3
Pulmonary	7	12	8
Endocrine	5	8	6

*Group 1 = erythropoietin and preoperative autologous donation, Group 2 = erythropoietin alone, and Group 3 = preoperative autologous donation alone.

Twenty (8%) had an underlying inflammatory arthropathy (Table I). There were thirty-four unilateral total knee arthroplasties, forty bilateral total knee arthroplasties, and thirty-two unilateral total knee revision arthroplasties. There were also sixty-four unilateral total hip arthroplasties, twenty-six bilateral total hip arthroplasties, and forty-four total hip revision arthroplasties. There was no significant difference, with the numbers available, between the groups with regard to sex ratio, age, height, weight, or type of arthritis ($p = 0.3$). The baseline hemoglobin level in Group 2 (119 g/L) was slightly lower than those in Group 1 (126 g/L) and Group 3 (129 g/L); this difference was significant ($p < 0.05$). However, the difference in baseline hemoglobin levels between Group 1 (erythropoietin and preoperative autologous donation) and Group 3 (preoperative autologous donation alone) was not significant ($p = 0.2$) (Table II).

Results

In Group 1 (erythropoietin and preoperative autologous donation), the mean hemoglobin level was 126 g/L at baseline, increased to 134 g/L immediately preoperatively as a result of erythropoietin treatment, and then dropped to 109 g/L postoperatively. Nine (11%) of the eighty patients in this group received a transfusion of an average of 1.1 units of packed red blood cells because of a low pretransfusion hemoglobin level (average, 76 g/L). In Group 2 (erythropoietin alone), the mean hemoglobin level increased from 119 g/L at baseline to 138 g/L immediately preoperatively as a result of erythropoietin treatment, and then dropped to 103 g/L postoperatively. Twenty-two (28%) of the eighty patients received a transfusion of an average of 1.3 units of packed red blood cells as a result of a low pretransfusion hemoglobin level (average, 78 g/L). In Group 3 (preoperative autologous donation alone), the mean hemoglobin level was 129 g/L at baseline, dropped to

116 g/L immediately preoperatively, and then dropped to 95 g/L postoperatively. Twenty-six (33%) of the eighty patients received a transfusion of an average of 1.5 units of packed red blood cells because of a low pretransfusion hemoglobin level (average, 78 g/L). The difference in allogeneic transfusion rates between Groups 2 and 3 (28% compared with 33%) did not reach significance ($p = 0.07$). However, the transfusion rate of 11% in Group 1 was significantly lower than the rates in both Group 2 and Group 3 ($p < 0.05$) (Fig. 1).

Within each treatment group, hematological parameters and transfusion requirements varied according to procedure (Table II).

Patients in Group 1 were able to predonate 102 of the requested 120 units of autologous blood. Ninety-seven (95%) of the 102 units were transfused intraoperatively, and five units were discarded. Patients in Group 3 were able to predonate 104 of the requested 124 units of autologous blood. Of the 104 units, 101 (97%) were transfused intraoperatively and three units were discarded.

Complications

The use of erythropoietin in this cohort was generally well tolerated, with few adverse reactions. The adverse reactions that did occur included local skin irritation at the injection site in sixty-four (40%) of the 160 patients, constipation in forty-three (27%), pyrexia in fifty-one (32%), and nausea in forty-two (26%). The erythropoietin therapy was not discontinued for any patient because of these reactions. Postoperative complications included three wound hematomas (one of which required operative evacuation), two transient peroneal nerve palsies, one episode of postoperative atrial fibrillation, one case of pneumonia, and one pulmonary embolus. There were no deaths or episodes of congestive heart failure, stroke, or deep venous thrombosis.

TABLE II Hematological Changes and Transfusion Rates According to Type of Arthroplasty

Type of Arthroplasty*	No. of Patients	Hemoglobin Level (g/L)			Patients with Transfusion	
		Baseline	Preop.	Postop.	No.	Pretransfusion Hemoglobin Level (g/L)
Group 1						
Unilat. total knee	15	123	132	126	0	0
Bilat. total knee	10	127	134	103	3	77
Unilat. rev. total knee	10	126	137	107	2	79
Unilat. total hip	18	128	136	110	1	74
Bilat. total hip	13	122	128	101	2	75
Unilat. rev. total hip	14	128	139	104	1	74
Total	80				9 of 80	
Mean (range)		126 (93-140)	134 (107-156)	109 (74-128)		76
Group 2						
Unilat. total knee	6	123	137	109	1	79
Bilat. total knee	20	123	135	101	7	78
Unilat. rev. total knee	14	120	139	111	4	79
Unilat. total hip	23	117	139	104	3	76
Bilat. total hip	3	109	132	91	0	0
Unilat. rev. total hip	14	121	145	103	7	77
Total	80				22 of 80	
Mean (range)		119 (83-140)	138 (102-161)	103 (73-137)		78
Group 3						
Unilat. total knee	13	139	132	102	1	77
Bilat. total knee	10	123	110	89	5	78
Unilat. rev. total knee	8	126	109	96	4	79
Unilat. total hip	23	127	121	97	4	78
Bilat. total hip	10	124	115	90	4	77
Unilat. rev. total hip	16	127	111	93	8	78
Total	80				26 of 80	
Mean (range)		129 (100-139)	116 (95-125)	95 (76-119)		78

*Group 1 = erythropoietin and preoperative autologous donation, Group 2 = erythropoietin alone, and Group 3 = preoperative autologous donation alone.

Discussion

Although multiple reports have shown the efficacy of erythropoietin for reducing allogeneic transfusion rates⁹⁻¹⁷, to our knowledge this is the first report showing such efficacy in patients treated at a single institution⁹⁻¹⁷. In addition, some previous reports included multiple orthopaedic procedures or only primary arthroplasties¹⁰⁻¹³, whereas the majority of the arthroplasties (59%) in the current series were bilateral or revision procedures. The overall allogeneic transfusion rate in the entire cohort was 24%. Use of erythropoietin in combination with preoperative autologous donation appeared to be the most effective method for reducing exposure to allogeneic blood, with a transfusion rate of 11%. Erythropoietin alone and preoperative autologous donation alone appeared to be similar to each other with regard to their effects on allogeneic blood exposure, with transfusion rates of 28% and 33%, respectively. Within the three treatment groups, there was an association between the particular procedure and the allogeneic transfusion rate. In

Group 1, the allogeneic transfusion rate for the patients treated with unilateral primary arthroplasty was 4% compared with 17% for those treated with a bilateral or revision procedure ($p < 0.05$). In Group 2, the transfusion rate for the patients treated with a unilateral primary procedure was 14%, which was significantly lower than the 35% rate for those treated with bilateral or revision arthroplasty ($p < 0.05$). In Group 3, the difference in the transfusion rates between the patients treated with a unilateral primary arthroplasty and those treated with a bilateral or revision arthroplasty was even greater: 15% compared with 47% ($p < 0.05$) (Table III).

Bierbaum et al.²⁶ reported the transfusion requirements for 9482 patients who had a total hip or knee arthroplasty in a large multicenter series that included a large number of bilateral and revision arthroplasties. However, there were no bilateral total hip arthroplasties in the series. Three hundred and thirty orthopaedic surgeons participated in the study. Allogeneic transfusion was required in 37% of the patients who had

TABLE III Allogeneic Transfusion Rates*

	No. of Patients	% (No.) of Patients with Transfusion
Group 1†	80	11% (9)
Unilat. primary arthroplasty	33	4% (1)
Bilat. and revision arthroplasty	47	17% (8)
Group 2†	80	28% (22)
Unilat. primary arthroplasty	29	14% (4)
Bilat. and revision arthroplasty	51	35% (18)
Group 3†	80	33% (26)
Unilat. primary arthroplasty	36	15% (5)
Bilat. and revision arthroplasty	44	47% (21)

*Group 1 = erythropoietin and preoperative autologous donation, Group 2 = erythropoietin alone, and Group 3 = preoperative autologous donation alone. †There was a significant difference between the transfusion rate in Group 1 and those in Groups 2 and 3 ($p < 0.05$).

a revision total hip arthroplasty (mean, 2.5 units), 28% who had a bilateral total knee arthroplasty (mean, 2.2 units), and 21% who had a revision total knee arthroplasty (mean, 2.3 units). The allogeneic transfusion rates were significantly higher in patients who had not predonated blood, with rates of 59%, 57%, and 30%, respectively.

In a study of preoperative autologous donation before hip replacement, Billote et al.²⁷ recently reported an allogeneic transfusion rate of zero. The trigger for transfusion in that series was a hemoglobin level of 70 g/L in healthy patients and 80 g/L in patients with comorbidities. The hemoglobin level at the time of discharge was 70 or 80 g/L in 15% of the patients who had not predonated blood. Other clinicians might consider that group of patients to be good candidates for transfusion. The allogeneic transfusion rates in the current series are more in line with those in other previously published reports^{9,10,12-18,20-24,28-31}.

In this series, erythropoietin appeared to minimize the development of perioperative anemia, a complication that has been previously noted in association with preoperative autologous donation programs². In other words, patients were able to predonate autologous blood without apparent adverse consequence. In the current study, the immediate preoperative hemoglobin level increased by 8 g/L, compared with the baseline value, in the group treated with erythropoietin and preoperative autologous donation, whereas it decreased by 13 g/L in the group treated with preoperative autologous donation alone.

Erythropoietin was well tolerated by our patients, and the four-dose regimen, as described by Goldberg et al.¹⁰, was also well received. There were a number of minor adverse reactions, the most common of which included a skin reaction at the injection site, pyrexia, constipation, and nausea. The erythropoietin therapy was not discontinued for any patient because of an adverse reaction. All patients who were treated with erythropoietin received the first dose, along with an initial dose of intravenous iron, in the hematologist's office. The arrangements for the subsequent doses of erythropoietin were patient-specific. A number of patients were able to give themselves the injections, whereas others received the medication

with the assistance of a relative, neighbor, family physician, or visiting nurse or on a return visit to the hematologist. On the basis of a survey, it appeared that the majority of patients were at least partially compliant with regard to taking doses of oral iron supplementation.

In terms of safety, there was only one thromboembolic event, which was a pulmonary embolus in a patient with systemic lupus erythematosus, and one episode of postoperative atrial fibrillation, which occurred in a patient with a history of paroxysmal atrial fibrillation. Other complications, probably not related to erythropoietin use, included three wound hematomas, two transient peroneal nerve palsies, and one case of pneumonia.

Possible flaws of this study include the open-label parallel-group design. In addition, only the operating surgeon was blinded regarding whether the patient had received erythropoietin. The cohort was also a consecutive series and, as such, subject to the inherent limitations associated with such series.

In conclusion, erythropoietin combined with preoperative autologous blood donation lowers allogeneic blood requirements more effectively than does either erythropoietin or preoperative autologous donation alone in patients undergoing total joint arthroplasty. ■

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