

Erythropoietin with Iron Supplementation To Prevent Allogeneic Blood Transfusion in Total Hip Joint Arthroplasty

A Randomized, Controlled Trial

Brian G. Feagan, MD; Cindy J. Wong, MSc; Alexandra Kirkley, MD; D.W.C. Johnston, MD; Frank C. Smith, MD; Paul Whitsitt, MD; Susan L. Wheeler, RN; and Catherine Y. Lau, PhD

Background: The optimum regimen of epoetin alfa for prevention of allogeneic blood transfusion is unknown.

Objective: To determine whether a modified regimen of epoetin alfa reduces allogeneic blood transfusion in patients undergoing hip arthroplasty.

Design: Randomized, double-blind, multicenter trial comparing two modified dose regimens of epoetin alfa with placebo.

Setting: 13 teaching hospitals and 4 community hospitals in Canada.

Patients: 201 patients undergoing primary hip arthroplasty who had a hemoglobin concentration of 98 to 137 g/L and did not predonate blood.

Intervention: Patients were assigned in a 3:5:5 ratio to receive four weekly doses of epoetin alfa, 40 000 U (high-dose; $n = 44$) or 20 000 U (low-dose; $n = 79$), or placebo ($n = 78$), starting 4 weeks before surgery. All patients received oral iron supplementation, 450 mg/d, for 42 or more days before surgery.

Measurements: The primary end point was allogeneic transfusion.

Secondary end points were thromboembolic events and change in reticulocyte count and hemoglobin concentration.

Results: Both modified epoetin alfa regimens significantly reduced the need for allogeneic transfusion: Five (11.4%) patients in the high-dose group ($P = 0.001$) and 18 (22.8%) patients in the low-dose group ($P = 0.003$) had transfusion, compared with 35 (44.9%) patients in the placebo group. The hematologic response was substantial in patients who received epoetin alfa. In the high-dose group, low-dose group, and placebo group, the preoperative increase in reticulocyte count was 58.8, 37.0 and 1.8×10^9 cells/L ($P < 0.001$), respectively, and the increase in hemoglobin concentration was 19.5, 17.2, and 1.2 g/L ($P < 0.001$). The incidence of thromboembolic events did not differ among groups.

Conclusions: Both modified epoetin alfa regimens were effective compared with placebo in reducing allogeneic transfusion in patients undergoing hip arthroplasty. Patients who received high-dose epoetin alfa had the lowest transfusion rate.

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For author affiliations, current addresses, and contributions, see end of text.

Total hip joint arthroplasty is frequently associated with transfusion of allogeneic blood (1, 2). Although serologic screening has reduced the risk for viral infection to a low level (3, 4), the public is highly concerned about this potential complication of transfusion (5). Therefore, further refinement of strategies to avoid exposure to allogeneic blood is needed. The most commonly used preventive strategy is autologous blood donation (6). Blood is collected from the patient before surgery and is reinfused if transfusion is necessary. In the past decade, this maneuver, which reduces exposure to pathogens and red cell alloimmunization, has become a standard of care in orthopedic surgery (7, 8). However, autologous blood donation has several disadvantages. First, donation and banking of autologous blood are inconvenient to patients (9, 10). Second, phlebotomy increases the prevalence of postoperative anemia and transfusion (either autologous or allogeneic) (11). Third, use of autologous blood is not without risk (12, 13). Bacterial contamination of predonated blood (14)

and major transfusion reactions (due to administrative error) (15) are rare but may be life-threatening. Finally and most important, many patients are not eligible for predonation because of concomitant medical conditions (16).

Erythropoietin, a glycoprotein produced by the kidney, stimulates production of red blood cells from the bone marrow (17). Administration of recombinant human erythropoietin (epoetin alfa) reduces the risk for allogeneic blood transfusion in patients undergoing total hip joint arthroplasty (18, 19). Factors that influence the response to epoetin alfa include the dose and timing of treatment (20), coadministration of iron (21, 22), and baseline hemoglobin concentration (23). Although several different preoperative regimens have been described, the regimen approved by the U.S. Food and Drug Administration consists of four subcutaneous injections of epoetin alfa, 600 U/kg of body weight, administered before surgery (weeks -3 , -2 , and -1 and the day of surgery) (24). Thus, a person weighing 70 kg would require a total dose of 168 000 U.

On the basis of subgroup analysis from a previous study (18), we hypothesized that a high dose of oral iron used in conjunction with a more prolonged epoetin alfa dosing schedule might produce a better hematologic response than that obtained with the standard regimen. We therefore evaluated the efficacy of two different epoetin alfa dose regimens.

METHODS

Patients

The study was a double-blind, randomized, parallel-group, multicenter clinical trial comparing the efficacy of epoetin alfa (Eprex, Janssen-Ortho Inc., Toronto, Ontario, Canada) with placebo in adult patients undergoing total hip joint arthroplasty. The trial was conducted at 13 teaching and 4 community hospitals in Canada from May 1996 to April 1999. The protocol was approved by the institutional review board of each participating center.

Eligible patients had a hemoglobin concentration of 98 to 137 g/L and did not predonate blood. At centers where an autologous blood donation program was available, blood predonation was discussed with patients; those who participated in the study were either ineligible for predonation because of medical contraindication or declined this option. Persons with rheumatoid arthritis, recent gastrointestinal or intracranial bleeding, iron deficiency, seizures, blood dyscrasias, or uncontrolled hypertension (diastolic blood pressure > 100 mm Hg) were excluded from the study. Patients who required revision arthroplasty or those in whom red cell salvage devices were considered essential were not enrolled. All patients gave written informed consent.

Baseline and Randomization Procedures

Participants were screened for eligibility 7 weeks before surgery. A history and physical examination were performed, and a complete blood count, iron studies, and blood chemistry were obtained; patients then began oral iron therapy. Six weeks before surgery, eligible patients were randomly assigned to one of three treatment groups. Randomization was performed according to a computer-generated schedule using a block size of 13 and an allocation ratio of 3:5:5 to the high-dose epoetin group, low-dose epoetin group, or placebo group, respectively.

Treatment Regimens

Patients began daily oral iron therapy at least 42 days before surgery and continued therapy until the day of hos-

pital discharge. Three capsules per day were recommended. In patients who were intolerant of iron, the number of capsules was reduced to the point of tolerability. The iron preparation prescribed was Niferex-150 (Schwarz Pharma, Mequon, Wisconsin). This polysaccharide-iron complex was selected because of its good tolerability and high bioavailability of elemental iron (150 mg per capsule) (25).

Patients received four weekly subcutaneous injections of placebo, high-dose epoetin alfa (40 000 U), or low-dose epoetin alfa (20 000 U) starting 4 weeks before surgery. The total possible dose was 160 000 U in the high-dose group and 80 000 U in the low-dose group. The study drug was withheld if the hemoglobin concentration was 150 g/L or more, systolic blood pressure was 200 mm Hg or more, or the diastolic blood pressure was 105 mm Hg or more. During the trial, the study coordinator at the data coordinating center, who was aware of the patient's hemoglobin concentration, authorized administration of study drug before each visit. This person had no contact with patients and did not assess outcomes.

Follow-up Schedule

Patients were evaluated 28, 21, 14, and 7 days before surgery. At these visits, vital signs and adverse events were recorded by the visiting nurse. Patients, surgeons, and nurses were unaware of treatment assignments and laboratory results. Hemoglobin concentration on the day of surgery was available to the surgeon and other health care personnel, but the reticulocyte count and the previous hemoglobin concentration were not. Blood loss was quantified by weighing sponges and measuring suction volume intraoperatively and subtracting the volume of the irrigation fluid. Patients were seen 1, 3, and 5 days after surgery; blood work was performed at these times. On the fifth day after surgery, patients underwent duplex ultrasonography (26, 27) to evaluate both legs for the presence of deep venous thrombosis.

Transfusion Policy

Transfusion of allogeneic blood was performed according to the usual practice of attending surgeons and anesthesiologists. We did not establish criteria for transfusion; however, the usual policy in Canada is not to perform transfusion in asymptomatic patients on the basis of a specific hemoglobin threshold. No patient donated or received autologous blood.

Outcome Measures

The primary outcome measure was occurrence of allogeneic blood transfusion. Secondary outcomes were changes in reticulocyte count and hemoglobin concentration. Adverse events were determined according to World Health Organization criteria (28). The proportion of patients who experienced thromboembolic disease (proximal or distal deep venous thrombosis and pulmonary embolus) and serious adverse events was compared among the treatment groups.

Statistical Analysis

Before the start of the study, retrospective chart review was performed to estimate the transfusion rate in patients undergoing hip arthroplasty ($n = 471$) who had characteristics similar to those of our patients. In those patients, the rate of allogeneic transfusion was 39% (95% CI, 34% to 43%). The reduction in the transfusion rate considered clinically important was 20%. On the basis of pharmacokinetic data, the higher dose of epoetin alfa was judged likely to be more efficacious (29) than the lower dose. Therefore, we estimated that the transfusion rate would decrease from 40% to 15% in the high-dose group and from 40% to 20% in the low-dose group. In accordance with these assumptions, we used an asymmetric randomization schedule that allocated a greater number of patients to the low-dose epoetin alfa and placebo groups (5 patients for every 3 that were allocated to the high-dose epoetin alfa group). This maneuver ensured adequate statistical power (80%) to compare the transfusion rate in the high-dose and low-dose groups with that in the placebo group. Since an allowance of 5% was made for unevaluable patients, 83 patients per group were required in the low-dose and placebo groups and 50 patients were needed in the high-dose group. Accordingly, the total sample size requirement was 216 patients.

All statistical analyses of efficacy measures were performed on an intention-to-treat basis, which was prospectively defined to include patients who had received at least one dose of study medication and subsequently underwent surgery within 1 week of the scheduled date. Separate chi-square tests were done to compare the proportion of patients who required transfusion in the placebo group with that among patients assigned to the low-dose epoetin alfa group or the high-dose epoetin alfa group. Bonferroni correction was used as a conservative method of adjusting for

multiple comparisons (30). Accordingly, an α error of 0.025 was considered to indicate statistical significance. Continuous outcome measures were compared by using analysis of variance. Logistic regression analyses were performed to explore the relationship between occurrence of transfusion and age, sex, weight, body mass index, predicted blood volume, baseline reticulocyte count, preoperative reticulocyte count, change in reticulocyte count, baseline hemoglobin concentration, preoperative hemoglobin concentration, change in hemoglobin concentration, baseline serum ferritin level, preoperative serum ferritin level, baseline serum iron level, preoperative serum iron level, number of days receiving iron therapy before surgery, baseline erythropoietin level, and treatment with epoetin alfa. Variables significant at the 0.10 level were examined further in a multivariate model by using a stepwise procedure. The proportion of patients with thromboembolic disease or other serious adverse events was compared by using a two-sided Fisher exact test.

Role of the Funding Source

The study was funded by Janssen-Ortho Inc., which had input into its design, conduct, and reporting.

RESULTS

Patients

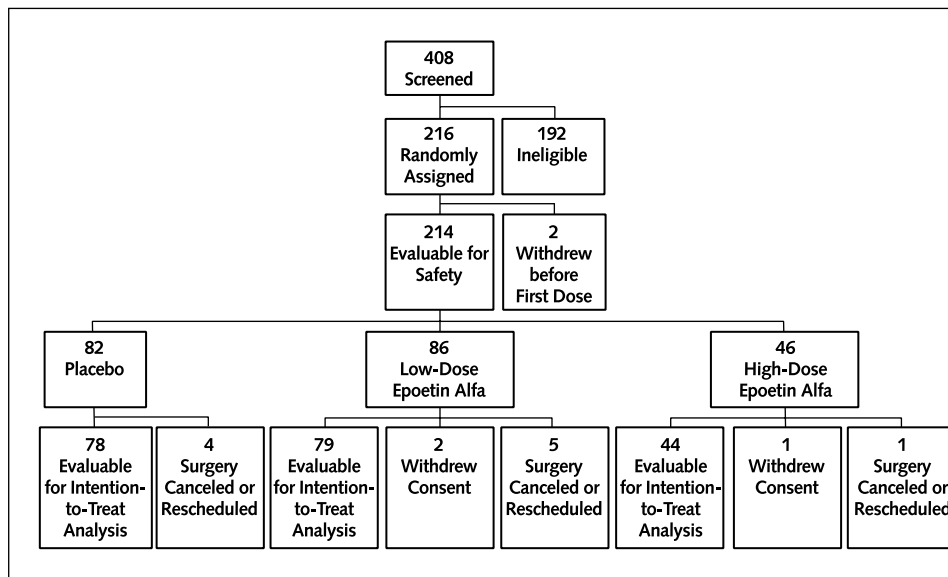
A total of 408 patients were evaluated for eligibility; of these, 216 were assigned to one of three treatment groups and 214 received study medication (Figure 1). The primary reason for ineligibility was a hemoglobin concentration that exceeded the maximum value (88% of the 192 ineligible cases). Ten patients did not undergo surgery within the specified time window, and 3 patients withdrew consent. Thus, 201 patients were included in the intention-to-treat analysis. Of these, 44 received high-dose epoetin alfa, 79 received low-dose epoetin alfa, and 78 received placebo.

Table 1 shows patient demographic and baseline characteristics. No statistically significant or clinically important differences were found among the treatment groups.

Adherence to Epoetin Alfa and Iron Therapy

No patients were lost to follow-up. Of the intention-to-treat group, 197 (98%) received all four scheduled doses of study medication. The remaining 4 patients received three of the four doses; one dose was withheld in 3 patients

Figure 1. Patient enrollment.



in the high-dose epoetin group because the hemoglobin concentration exceeded the maximum value allowed and in 1 patient in the low-dose epoetin group because of elevated blood pressure. More than 80% of the doses of study medication were received within 1 day of the scheduled date of dosing.

Iron therapy was well tolerated; 84% of patients took oral iron for at least 42 days before surgery. Almost all patients (198 [99%]) received oral iron for at least 35 days before surgery. The treatment groups did not differ in adherence to oral iron therapy.

Measures of iron metabolites are shown in Table 2. Of

note, the active treatment groups experienced a marked dose-related decrease in serum ferritin level.

Transfusion Requirements

The proportion of patients who received a blood transfusion is shown in Table 3. The mean hemoglobin concentration at the time of transfusion was 79.0 g/L in the high-dose epoetin group, 82.6 g/L in the low-dose epoetin group, and 76.9 g/L in the placebo group ($P = 0.165$). The rate of transfusion was 11.4% (5 of 44 patients) in the high-dose epoetin group and 22.8% (18 of 79 patients) in the low-dose epoetin group compared with 44.9% (35 of 78 patients) in the placebo group ($P = 0.001$ and $P = 0.003$, respectively, for treatments vs. placebo). The greatest difference among the treatment groups was observed for postoperative transfusions. Patients who underwent transfusion received approximately 2 units of allogeneic blood irrespective of study group assignment.

Hematologic Response

Patients who received either epoetin alfa regimen showed a rapid increase in the reticulocyte count and hemoglobin concentration (Figure 2). By the day of surgery, the greatest increase in reticulocyte count had occurred in patients who received high-dose epoetin alfa (58.8×10^9 cells/L compared with 37.0×10^9 cells/L in the low-dose

Table 1. Patient Demographic and Baseline Characteristics*

Characteristic	Placebo Group (n = 78)	Low-Dose Epoetin Alfa Group (n = 79)	High-Dose Epoetin Alfa Group (n = 44)
Age, y	67.8 ± 11.9	68.9 ± 10.8	67.3 ± 11.0
Men, %	12.8	7.6	11.4
Baseline hemoglobin concentration, g/L	125.7 ± 7.0	125.1 ± 8.8	126.1 ± 7.6
Predicted blood volume, L	4.1 ± 0.8	4.1 ± 0.6	4.3 ± 0.8
Body mass index, kg/m ²	29.0 ± 5.6	27.6 ± 6.0	29.9 ± 6.7
Serum ferritin level, µg/L	113.0 ± 113.5	105.3 ± 119.3	88.9 ± 68.5
Primary osteoarthritis, %	80.8	86.1	88.6
Intraoperative blood loss, mL	579 ± 282	583 ± 279	588 ± 384

* Values with the plus/minus sign are the mean ± SD.

Table 2. Iron Stores*

Substance	Placebo Group (n = 78)	Low-Dose Epoetin Alfa Group (n = 79)	High-Dose Epoetin Alfa Group (n = 44)
Serum ferritin level, $\mu\text{g/L}$			
Baseline	113.0 \pm 113.5	105.3 \pm 119.3	88.9 \pm 68.5
Before surgery	113.0 \pm 113.0	47.9 \pm 99.5	29.8 \pm 27.9
Discharge	227.9 \pm 189.9	165.6 \pm 119.4	145.2 \pm 86.4
Serum iron concentration, $\mu\text{mol/L}$ ($\mu\text{g/dL}$)			
Baseline	11.2 \pm 4.5 (62.3 \pm 25.4)	11.9 \pm 4.1 (66.3 \pm 22.8)	11.3 \pm 4.7 (63.1 \pm 26.4)
Before surgery	11.2 \pm 4.2 (62.5 \pm 23.5)	9.4 \pm 7.3 (52.7 \pm 40.9)	8.4 \pm 9.2 (46.9 \pm 51.3)
Discharge	6.7 \pm 3.5 (37.5 \pm 19.8)	6.0 \pm 3.5 (33.3 \pm 19.8)	5.7 \pm 3.6 (31.9 \pm 20.1)
Total iron-binding capacity, $\mu\text{mol/L}$ ($\mu\text{g/dL}$)			
Baseline	52.6 \pm 9.6 (293.9 \pm 53.8)	52.8 \pm 10.8 (295.0 \pm 60.4)	52.1 \pm 10.4 (290.9 \pm 58.0)
Before surgery	51.8 \pm 10.3 (289.0 \pm 57.7)	56.2 \pm 11.6 (313.7 \pm 65.0)	56.9 \pm 12.2 (317.9 \pm 68.3)
Discharge	40.3 \pm 9.1 (225.0 \pm 50.8)	40.4 \pm 9.0 (225.4 \pm 50.0)	45.9 \pm 13.4 (256.5 \pm 74.7)

* Values are the mean \pm SD.

epoetin group [$P = 0.003$] and 1.8×10^9 cells/L in the placebo group [$P < 0.001$]). Clinically meaningful increases in hemoglobin concentration were observed in the high-dose (19.5 g/L) and low-dose (17.2 g/L) epoetin alfa groups, whereas little change was noted in the placebo group (1.2 g/L) ($P < 0.001$). After surgery, the hemoglobin concentration decreased by approximately the same amount in all three groups (-36.1 g/L in the high-dose epoetin alfa group [CI, -39.6 to -32.5 g/L], -36.5 g/L in the low-dose epoetin alfa group [CI, -39.1 to -34.0 g/L], and -35.1 g/L in the placebo group [CI, -37.5 to -32.8 g/L]).

Predictors of Transfusion

In univariate analyses, older age, lower weight, lower predicted blood volume, lower preoperative reticulocyte count, smaller change in reticulocyte count, lower baseline and preoperative hemoglobin concentration, smaller change

in hemoglobin concentration, and lack of treatment with preoperative epoetin alfa were associated with occurrence of transfusion ($P < 0.10$). In the multivariate model, age ($P = 0.012$), predicted blood volume ($P = 0.023$), preoperative hemoglobin concentration ($P = 0.001$), and preoperative reticulocyte count ($P = 0.013$) remained significant predictors of transfusion (Table 4).

Thromboembolic Disease and Adverse Events

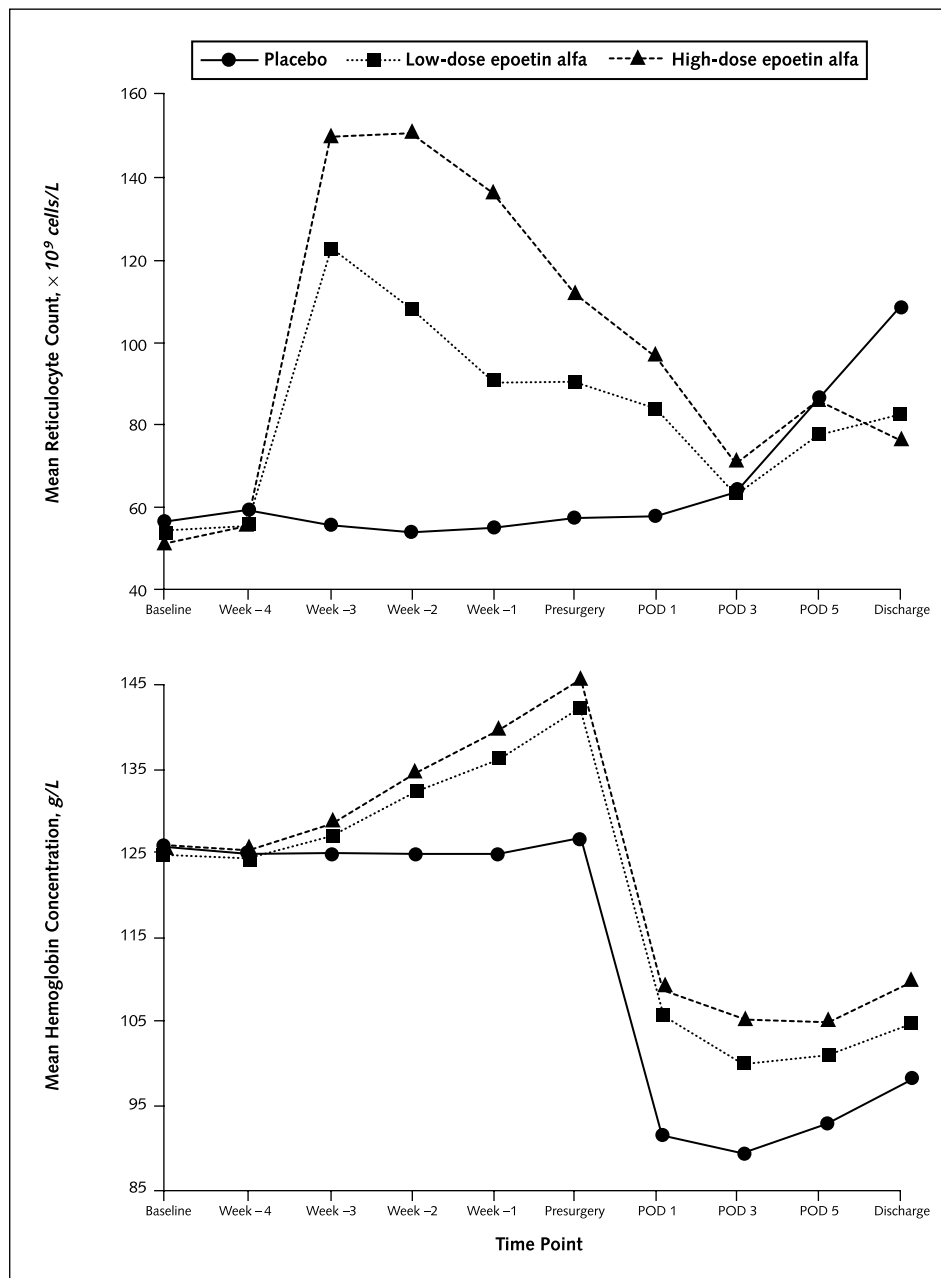
Ninety-two percent of patients underwent duplex ultrasonography. The incidence of thromboembolic disease did not differ among the three treatment groups (Table 5). One pulmonary embolus was reported in the placebo group. The proportion of patients who experienced any serious adverse event was similar in the three study groups: 8.5% in the placebo group, 3.5% in the low-dose epoetin alfa group, and 6.5% in the high-dose epoetin alfa group.

Table 3. Transfusion Requirements*

Transfusion Characteristics	Placebo Group (n = 78)	Low-Dose Epoetin Alfa Group (n = 79)	High-Dose Epoetin Alfa Group (n = 44)
Patients who received transfusion (95% CI), %			
Intraoperatively	9.0 (2.6–15.3)	8.9 (2.6–15.1)	4.5 (0–10.7)
Postoperatively	39.7 (28.9–50.6)	15.2 (7.3–23.1)	9.1 (0.6–17.6)
Any transfusion	44.9 (33.8–55.9)	22.8 (13.5–32.0)	11.4 (2.0–20.7)
Blood transfused among all patients, units			
Intraoperatively	0.1 \pm 0.4	0.1 \pm 0.4	0.1 \pm 0.3
Postoperatively	0.8 \pm 1.1	0.3 \pm 0.8	0.2 \pm 0.6
Any transfusion	1.0 \pm 1.2	0.4 \pm 0.9	0.3 \pm 0.7
Blood transfused among transfused patients only, units			
Intraoperatively	1.4 \pm 0.5	1.3 \pm 0.5	1.5 \pm 0.7
Postoperatively	2.1 \pm 0.7	2.0 \pm 0.7	2.0 \pm 0.0
Any transfusion	2.1 \pm 0.8	1.8 \pm 0.8	2.2 \pm 0.4

* Values with the plus/minus sign are the mean \pm SD.

Figure 2. Reticulocyte count and hemoglobin concentration among patient groups.



POD = postoperative day.

DISCUSSION

A modified version of the standard epoetin alfa regimen produced excellent response to therapy. The lowest transfusion rate was achieved in the high-dose epoetin alfa group, in which 11.4% of patients required transfusion compared with 44.9% of placebo recipients (absolute risk

reduction, 33.5% [CI, 19.0% to 48.0%]; number needed to treat for benefit, 3.0). Moreover, the low-dose regimen, which used only 80 000 U of epoetin alfa in total (compared with 160 000 U in the high-dose regimen), was also associated with a significant reduction in the rate of transfusion (22.8% of patients who received the low-dose regi-

Table 4. Predictors of Transfusion

Predictor	Risk Ratio (95% CI)*
Older age (per decade)	1.6 (1.1–2.5)
Lower predictive volume (per L)	2.0 (1.1–3.6)
Lower preoperative hemoglobin concentration (per 10 g/L)	1.7 (1.3–2.4)
Lower preoperative reticulocyte count (per 20×10^9 cells/L)	1.4 (1.1–1.7)

* Calculated by using a multiple logistic regression model.

men compared with 44.9% of placebo recipients) (absolute risk reduction, 22.1% [CI, 7.7% to 36.5%]; number needed to treat for benefit, 4.5).

The increase in hemoglobin concentration observed with use of the modified regimen (19.5 g/L in the high-dose epoetin alfa group and 17.2 g/L in the low-dose epoetin alfa group) was greater than that demonstrated in other controlled trials of perioperative epoetin alfa therapy. Goldberg and colleagues (24), who used the approved regimen of 600 U/kg once weekly for 3 weeks before surgery and on the day of surgery (an average total dose of 177 600 U) in patients undergoing total hip and knee joint arthroplasty who had a baseline hemoglobin concentration of 100 to 130 g/L, documented an increase in hemoglobin concentration of 14.4 g/L and reported an allogeneic transfusion rate of 19.4% in patients who underwent hip surgery. The modified regimen that we used probably produced a better bone marrow response than does the currently approved perioperative epoetin alfa regimen.

We made three modifications to the standard regimen. First, therapy was initiated 4 weeks before surgery rather than 3 weeks. Thus, additional time was available for optimal response by bone marrow. Second, a greater total dose of oral iron was given. Our patients received 450 mg of elemental iron daily compared with approximately 200 mg/d in the standard regimen. Although pharmacokinetic studies have shown that availability of iron is an important determinant of the response to epoetin alfa (31), the amount of oral iron that can be administered is often limited by development of gastrointestinal symptoms (32). The iron preparation that we prescribed was well tolerated; 84% of the patients adhered to therapy and only 2% experienced symptoms that necessitated a reduction in dose or discontinuation of therapy. We speculate that administration of a high dose of oral iron may be the primary determinant of the response to erythropoietin. In support of this notion, we observed a marked dose-dependent de-

crease in serum ferritin concentration, which reflects the high demand that epoetin alfa therapy places on body iron stores. Finally, we omitted the dose of epoetin alfa on the day of surgery. In our opinion, dosing at this time is unlikely to be effective for prevention of transfusion, given that the majority of blood is transfused in the first 3 days after surgery.

These considerations highlight an important limitation of this study. Because multiple alterations to the standard regimen were made, we cannot identify which one was primarily responsible for the enhanced treatment response. Further refinements to the regimen may result in even greater efficacy. Another potential limitation is that we did not establish guidelines for allogeneic transfusion at the participating centers. Nevertheless, transfusion practice during this trial reflected usual clinical practice.

Which of the two epoetin alfa regimens studied in this trial is to be recommended? The reduction in transfusion was significant in both epoetin alfa groups compared with placebo. However, the transfusion rate was lowest in patients who received the high-dose regimen. Moreover, the increase in reticulocyte count and hemoglobin concentration was greatest in the high-dose group, and the multivariate model identified both of these variables as significant predictors of the occurrence of transfusion. Therefore, we speculate that the superior bone marrow response observed in the high-dose group might have accounted for the additional reduction in transfusion. The observed difference was not statistically significant (11.4% in the high-dose

Table 5. Occurrence of Deep Venous Thrombosis and Pulmonary Embolism*

Event	Placebo Group (n = 78)	Low-Dose Epoetin Alfa Group (n = 79)	High-Dose Epoetin Alfa Group (n = 44)
	←————— n —————→		
Proximal DVT			
Symptomatic	1	3	1
Asymptomatic	0	0	0
Distal DVT			
Symptomatic	2	3	0
Asymptomatic	2	0	1
Any DVT			
Symptomatic	3	5	1
Asymptomatic	2	0	1
Pulmonary embolism	1	0	0
Any DVT or pulmonary embolism	6	5	2

* Values are the number of patients who experienced an event during the postoperative period. DVT = deep venous thrombosis.

group compared with 22.8% in the low-dose group; difference, 11.4 percentage points [CI, -1.8 to 24.6 percentage points]; $P = 0.119$); however, our study was not designed to compare the two active treatment regimens with respect to this outcome. Accordingly, the failure to find a significant difference in favor of the high-dose regimen may have resulted from inadequate statistical power. Performance of a test for trend demonstrated a significant association ($P < 0.001$) in favor of a higher epoetin alfa dose; however, this analysis was not prespecified, and this finding should be interpreted with caution. Although a relatively large clinical trial (168 patients per treatment group to demonstrate a difference between 11.4% and 22.8%) would be required to definitively determine which epoetin alfa regimen is optimal, we believe that such a study should be performed given that the cost of epoetin alfa therapy is an important consideration.

Although our study did not compare the epoetin alfa regimens with autologous blood donation, the low-dose regimen probably had efficacy similar to that of autologous blood donation for prevention of allogeneic transfusion, whereas the high-dose regimen may be superior (19). However, the majority of patients who participated in this study were ineligible for predonation or autologous blood donation was not accessible. Since administration of epoetin alfa is more convenient than predonation of blood, patients may favor the former intervention.

A major limitation of our study is that we did not assess the cost-effectiveness of the two epoetin alfa regimens. The retail cost of epoetin alfa is Can\$267.90 per 20 000-U vial and Can\$535.80 per 40 000-U vial. Accordingly, additional data from randomized, controlled trials, patient preference studies, and pharmacoeconomic studies are required before a credible recommendation about the optimal blood-sparing strategy can be made.

In the absence of such new data, our results show that epoetin alfa is an effective alternative for patients who cannot predonate blood. Since hypertension has been previously identified as a potential complication in patients with chronic renal failure who are receiving epoetin alfa (33), blood pressure should be monitored during the preoperative dosing period. Although previous studies have suggested a possible increased incidence of deep venous thrombosis in patients receiving epoetin alfa (18, 34), our data do not support this relationship. However, the study lacked sufficient statistical power to definitively exclude this possibility. Finally, the results of the multivariate anal-

ysis, which attempted to identify predictors of allogeneic transfusion, were not unexpected. Previous studies have shown that predicted blood volume and age are important determinants of the risk of transfusion (2, 35). Moreover, since both preoperative hemoglobin concentration and reticulocyte count are highly correlated with epoetin alfa therapy, it is not surprising that they were identified as being inversely correlated with occurrence of transfusion.

In conclusion, the modifications that we made to the approved epoetin alfa regimen enhanced the response to erythropoietin and significantly reduced the risk for allogeneic blood transfusion. Internists who are involved in the preoperative management of patients undergoing total hip joint arthroplasty must understand the importance of both the timing and dose of epoetin alfa and the potentially vital role of concomitant iron therapy.

APPENDIX: PARTICIPATING CENTERS, NUMBER OF PATIENTS ENROLLED, AND INVESTIGATORS AND SITE COORDINATORS

University of Alberta Hospitals, Edmonton: 48 patients (W. Johnston, L. Beaupre, L. Schaump, D. Bohonis, K. Greaves); London Health Sciences Centre, London: 38 patients (B. Feagan, A. Kirkley, C. Rorabeck, R. Bourne, J. Murkin, R. McCalden, S. MacDonald, C. McCabe); Sir William Osler Health Institute, Hamilton: 38 patients (F. Smith, N.I. Dale, L. Reynolds); LakeRidge Health, Oshawa: 29 patients (P. Whitsitt, N. Rochon, D. Taylor); Kelowna General Hospital, Kelowna: 12 patients (T.A. O'Farrell, D. Boyce, W. Pisesky, G. O'Connor, E. LeNoble, M. Mantle); Kingston General Hospital, Kingston: 11 patients (D. Bond, K. Turner, P. Bond, K. Swilzer); Hôpital Sacre-Coeur, Montreal: 10 patients (G.H. Laflamme, B. Pynn); The Moncton City Hospital, Moncton: 9 patients (G. Dow, J. Steeves, A. Clark, G. Pavlatos-Jones, C. MacLoughlin); Pavillon Saint-François d'Assise: 8 patients (P. Laliberte, A. Grenier, J. Chabot, M. Lortie); Hôpital Hotel-Dieu de Montreal, Montreal: 3 patients (C. Godin, B. Pynn); St. Michael's Hospital: 2 patients (J. Waddell, J. Morton); The Toronto Hospital, Toronto: 2 patients (A. Sandler, Z. Kaszas); St. Paul's Hospital, Vancouver: 2 patients (B. Warriner, D. Werry, C. Metcalfe); Sunnybrook Health Sciences Centre, Toronto: 1 patient (M. Tile, V. Dubrovskis); Ottawa Civic Hospital, Ottawa: 1 patient (R. Garnett, B. Krepski, N. Cicutti); Montreal Jewish General Hospital, Montreal: 1 patient (O. Huk, B. Pynn); Humber

River Regional Hospital, Weston: 1 patient (J. Wilson, N. Johnston, R. Mulock).

Data Co-ordinating Centre: B. Sarazin, E. Liddiard, B. Bergman, W. Johnson, London Clinical Trials Research Group.

From University of Western Ontario and London Clinical Trials Research Group, London, Ontario; University of Alberta, Edmonton, Alberta; Sir William Osler Health Institute, Hamilton, Ontario; LakeRidge Health Oshawa, Oshawa, Ontario; and Janssen-Ortho Inc., Toronto, Ontario, Canada.

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Requests for Single Reprints: Brian G. Feagan, MD, London Clinical Trials Research Group, The John P. Robarts Research Institute, Box 5015, 100 Perth Drive, London, Ontario N6A 5K8, Canada.

Current Author Addresses: Dr. Feagan and Ms. Wong: London Clinical Trials Research Group, The John P. Robarts Research Institute, Box 5015, 100 Perth Drive, London, Ontario N6A 5K8, Canada.

Dr. Kirkley: Fowler Kennedy Sport Medicine Clinic, 1151 Richmond Street, London, Ontario N6A 3K7, Canada.

Dr. Johnston: College Plaza, 506-8215 112 Street NW, Edmonton, Alberta T6G 2C8, Canada.

Dr. Smith: Sir William Osler Health Institute, 105-565 Sanatorium Road, Hamilton, Ontario L9C 7N4, Canada.

Dr. Whitsitt: Oshawa Clinic, 117 King Street East, Oshawa, Ontario L1H 1B9, Canada.

Ms. Wheeler and Dr. Lau: Janssen-Ortho Inc., 19 Green Belt Drive, Toronto, Ontario M3C 1L9, Canada.

Author Contributions: Conception and design: B.G. Feagan, C.J. Wong, A. Kirkley, C.Y. Lau.

Analysis and interpretation of the data: B.G. Feagan, C.J. Wong, C.Y. Lau.

Drafting of the article: B.G. Feagan, C.J. Wong.

Critical revision of the article for important intellectual content: B.G. Feagan, C.J. Wong, C.Y. Lau.

Final approval of the article: B.G. Feagan, C.J. Wong, C.Y. Lau.

Provision of study materials or patients: B.G. Feagan, A. Kirkley, D.W.C. Johnston, F.C. Smith, P. Whitsitt, S.L. Wheeler, C.Y. Lau.

Statistical expertise: C.J. Wong.

Obtaining of funding: B.G. Feagan, S.L. Wheeler, C.Y. Lau.

Administrative, technical, or logistic support: S.L. Wheeler.

Collection and assembly of data: C.J. Wong, S.L. Wheeler.

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