

## Epoetin Alfa Reduces Need for Transfusions in Hip Arthroplasty

Feagan BG, Wong CJ, Kirkley A, et al. Erythropoietin with iron supplementation to prevent allogenic blood transfusion in total hip joint arthroplasty. A randomized control trial. *Ann Intern Med* 2000;133:845-54.

### Study Overview

**Objective.** To determine if a regimen of erythropoietin (epoetin alfa) reduces the need for allogenic blood transfusion in patients undergoing total hip arthroplasty.

**Design.** Randomized, double-blind trial.

**Setting and participants.** 408 adult patients scheduled for primary hip arthroplasty were screened from 13 teaching hospitals and 4 community hospitals in Canada. Of the patients screened, 216 were randomized and 192 were ineligible to participate. Subjects selected for randomization had a hemoglobin concentration of 98 to 137 g/L and had not predonated blood. Patients were excluded who had rheumatoid arthritis, recent gastrointestinal or intracranial bleeding, iron deficiency anemia, seizures, blood dyscrasia, or uncontrolled hypertension (diastolic blood pressure > 100 mm Hg). The study was conducted from May 1996 to April 1999.

**Intervention.** Six weeks before surgery, eligible patients were randomized in a 3:5:5 ratio to receive 4 weekly subcutaneous injections of high-dose epoetin alfa (40,000 U;  $n = 44$ ), low-dose epoetin alfa (20,000 U;  $n = 79$ ), or placebo ( $n = 78$ ). Treatment administration began 4 weeks before surgery. Total possible doses of the study drug were 160,000 U in the high-dose group and 80,000 U in the low-dose group. All patients began oral iron therapy (450 mg/day) at least 42 days before surgery and continued therapy until the day of hospital discharge. Patients were evaluated at 28, 21, 14, and 7 days prior to surgery and followed up at 1, 3, and 5 days after surgery.

**Main outcome measures.** The primary outcome was the number of allogenic transfusions required by patients. Secondary outcomes were changes in hemoglobin and reticulocyte counts and number of adverse events, which included thromboembolism, deep venous thrombosis, or any other serious outcome.

**Main results.** Baseline patient characteristics were similar

among the 3 study groups. Subjects had a mean age of 67 years and a mean hemoglobin concentration of 125 g/L. The mean ferritin level in the high-dose group ( $88.9 \pm 68.5$   $\mu\text{g/L}$ ) was slightly lower than that seen in the low-dose group ( $105.3 \pm 119.3$   $\mu\text{g/L}$ ) and placebo group ( $113.0 \pm 113.5$   $\mu\text{g/L}$ ). Blood transfusion rates were 11.4% (5 patients) in the high-dose group and 22.8% (18 patients) in the low-dose group, compared with 44.9% (35 patients) in the placebo group; these results were statistically significant ( $P = 0.001$  and  $P = 0.003$ , respectively, for treatment versus placebo). By the day of surgery, the greatest increase in reticulocyte count occurred in patients receiving high-dose treatment ( $58.8 \times 10^9$  cells/L versus  $37.0 \times 10^9$  cells/L in low-dose patients [ $P = 0.003$ ] and  $1.8 \times 10^9$  cells/L in controls [ $P < 0.001$ ]). Clinically meaningful increases in hemoglobin concentration were seen in the high-dose (19.5 g/L) and low-dose (17.2 g/L) treatment groups, while little change occurred in the placebo group (1.2 g/L) ( $P < 0.001$ ). Duplex ultrasonography was performed on 92% of all patients to check for deep venous thrombosis; these tests revealed no difference in thrombosis rates among study groups. Rates of serious adverse events were also similar (8.5% in the placebo group, 3.5% in the low-dose group, and 6.5% in the high-dose group).

### Conclusion

Both the low- and high-dose epoetin alfa regimens were effective in reducing allogenic transfusion rates in patients undergoing hip arthroplasty. The lowest transfusion rate was achieved among high-dose patients.

### Commentary

Allogenic transfusions after hip arthroplasty are very common and carry significant morbidity and mortality risks despite systemic screening for viral illness. Moreover, many individuals are not eligible for autologous transfusions. A previous Canadian study showed that epoetin can reduce the need for blood transfusions among patients undergoing elective hip replacement surgery [1]. This study by Feagan et al shows a clear improvement in hemoglobin levels with epoetin use, at both low and high doses, as well as an asso-

ciated reduction in transfusions needed (absolute risk reduction, 33.5% [95% confidence interval (CI), 19.0% to 48.0%] in the high-dose group and 22.1% [95% CI, 7.7% to 36.5%] in the low-dose group compared with placebo). The number needed to treat to prevent any transfusion in the high-dose group was very low (3.0), and the risk of serious side effects seemed similar to that seen in the placebo group. Feagan and colleagues did measure risk of thromboembolic disease; however, risks of other potential side effects resulting from epoetin administration (eg, hypertension) were not assessed [2]. The risk of clotting, which is usually very low (less than 1%), is a serious side effect, but the study may have been too small to show an increase in this risk.

The coadministration of iron supplements likely played a role in the large treatment effect observed with epoetin use. Investigators used a preparation (polysaccharide iron complex) that has good bioavailability. It remains unclear whether similar increases in hemoglobin concentrations would have been achieved with other iron preparations that are less well tolerated. The authors acknowledge that a major weakness of their study lies in the fact that the cost-effectiveness of study treatment was not measured; this question would merit further study. Additional research should also be conducted to confirm the safety of epoetin

therapy and to determine which regimen (high dose versus low dose) is more effective. Feagan et al's study did not have enough statistical power to address this issue, although a trend toward fewer transfusions in the high-dose group was observed. Finally, it would be interesting to determine if therapy similar to the study treatment could be applied to other surgical procedures requiring transfusions (eg, abdominal aorta repair, coronary artery bypass surgery).

### Applications for Clinical Practice

Epoetin therapy can reduce the need for transfusions in patients who require arthroplasty. Although a recommendation to make this standard treatment would be premature, epoetin use should be considered for patients who cannot receive autologous transfusions.

### References

1. Effectiveness of perioperative recombinant human erythropoietin in elective hip replacement. Canadian Orthopedic Perioperative Erythropoietin Study Group. *Lancet* 1993;341:1227-32.
2. Goodnough LT, Monk TG, Andriole GL. Erythropoietin therapy. *N Engl J Med* 1997;336:933-8.

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