A Randomized, Parallel-Group, Open-Label Trial of Recombinant Human Erythropoietin vs Preoperative Autologous Donation in Primary Total Joint Arthroplasty

Effect on Postoperative Vigor and Handgrip Strength

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Abstract: This randomized trial assessed the effect of recombinant human erythropoietin (EPO) vs preoperative autologous donation (PAD) on postoperative vigor and handgrip strength in patients undergoing primary total joint arthroplasty. Adults with baseline hemoglobin level of 11 to 14 g/dL received EPO (600 IU/kg once weekly for 4 doses, n = 130) or PAD (n = 121) before primary, unilateral hip or knee arthroplasty. Mean changes in vigor score and handgrip strength from baseline were not significantly different between treatment groups. Multivariate analyses found a significant treatment effect favoring EPO over PAD for vigor, but not for handgrip strength. Patients in the EPO group had higher hemoglobin levels and required fewer transfusions. Both treatments were well tolerated. Additional study is needed to elucidate the influence of blood management strategies on postoperative vigor. **Key words:** epoetin alfa, preoperative autologous donation, vigor, strength, transfusion.

Total joint arthroplasty usually leads to significant blood loss and may result in allogeneic blood transfusion [1-3]. To avoid the substantial risks associated with allogeneic transfusion, patients frequently donate autologous blood before elective orthopedic surgery [2,3]. However, donation and transfusion of autologous blood are not risk free [4]. Although erythropoiesis is stimulated by phlebotomy, the blood loss that results from preoperative autologous donation (PAD) usually exceeds the blood production, worsening perioperative anemia [5]. Febrile nonhemolytic and allergic reactions have been reported [6], and clerical errors may result in administration of the wrong blood to the wrong patient, resulting in catastrophic outcomes [7]. Furthermore, PAD is time consuming and may not be cost-effective [3,8,9]. Patients who donate blood preoperatively often do not receive transfusions perioperatively; thus, many units of autologous blood are wasted [3]. Donated blood

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that is not transfused during arthroplasty may account for hundreds of dollars in wasted costs [9]. In addition to these potential risks and limitations of donating autologous blood, many patients still require allogeneic transfusions after they receive autologous transfusions [3,10].

Erythropoietin is a glycoprotein hormone that stimulates red blood cell production in the bone marrow, and recombinant human erythropoietin (EPO) has an amino acid sequence identical to that of endogenous erythropoietin. Numerous studies have demonstrated the ability of EPO to increase hemoglobin levels and reduce the need for allogeneic blood transfusion in patients who undergo hip or knee arthroplasty [11-24]. Several other studies have established the ability of EPO to enhance energy and quality of life in patients with anemia associated with chronic kidney disease, human immunodeficiency virus treatment, or cancer chemotherapy [25,26], but similar studies have not been undertaken in patients having hip or knee arthroplasty. We previously reported that it is possible to measure postoperative vigor using a questionnaire that was designed specifically for this purpose [27]. Other authors have demonstrated the validity of measuring handgrip strength with hydraulic dynamometers [28]. This trial was conducted in patients scheduled to undergo primary, unilateral hip or knee arthroplasty to compare the effect of EPO vs PAD on postoperative vigor and handgrip strength.

Materials and Methods

This prospective, randomized, open-label, parallel-group trial was performed at 20 study sites in the United States (Appendix A). The protocol entitled "The Effect of PROCRIT on Hemoglobin and Hematocrit and the Relationship to Postoperative Function, Vigor and Strength in Patients Undergoing Primary Total Joint Arthroplasty: A Randomized, Parallel Group, Open-Label Trial" was approved by the institutional review board at each participating site. All patients provided written informed consent.

Adults 18 years or older were eligible to participate if they were scheduled for elective, unilateral, primary total joint arthroplasty of the hip or knee, and their pretreatment hemoglobin level was 11 g/dL or more and 14 g/dL or less. A preoperative lead time between 21 and 60 days was required, and patients needed to be physically able and willing to participate in a PAD program. Women were excluded if they were pregnant, and women of childbearing potential were required to practice an acceptable form of birth control during the study. Other exclusion criteria included uncontrolled hypertension, presence of seizure disorder, history of deep vein thrombosis, significant gastrointestinal bleeding in the previous 6 months, or clinically significant disease of the hematologic, cardiovascular, neurologic, pulmonary, endocrine, gastrointestinal, or genitourinary system that was not well controlled. All patients provided written informed consent to participate, and the protocol and consent forms were approved by the institutional review board at each site.

Investigators called an interactive voice response system to determine study treatment allocation for each eligible patient; the centralized randomization schedule was prepared with permuted blocks before the study. All treatments were administered without concealment. Patients who were assigned to treatment with EPO (PROCRIT, Ortho Biotech Products, LP, Bridgewater, NJ) received a subcutaneous injection of 600 IU/kg once weekly for 3 weeks preoperatively (on days 21, 14, and 7) and then within 24 hours postoperatively. Patients in the PAD group were to donate 1 U of blood before total knee arthroplasty, and 2 U of blood before total hip arthroplasty, as tolerated, beginning up to 28 days preoperatively. Patients were not permitted to receive both study treatments. Daily oral iron supplementation with a polysaccharide-iron complex or the equivalent of 300 mg elemental iron was given in both treatment groups.

During and after arthroplasty, it was recommended that blood transfusions should not be given if the patient had a hemoglobin level of 8 g/dL or more unless clinical symptoms or a documented history of cardiac disease warranted intervention. Investigators were instructed to use identical criteria for autologous and allogeneic blood transfusions. If a patient who donated autologous blood required a transfusion, the autologous blood was to be used before any transfusions of allogeneic blood. The hemoglobin level and the reason for administering blood were documented before every transfusion.

Baseline measures were collected 28 to 21 days before surgery and included patient demographics, hematologic parameters (hemoglobin, hematocrit, red blood cell count, white blood cell count, platelet count, and reticulocytes), vigor, and handgrip strength. Measures of hemoglobin, vigor, and handgrip strength were repeated within 24 hours before surgery, and then on postoperative day 2, postoperative day 4 or 5 (or at discharge if before day 4), and once between postoperative days 14 to 21. Vigor