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A randomized, double-blind, placebo-controlled study to assess the effect of recombinant human erythropoietin on functional outcomes in anemic, critically ill, trauma subjects: the Long Term Trauma Outcomes Study

Fred A. Luchette, M.D., M.Sc, F.A.C.S.[a,*], Michael D. Pasquale, M.D., F.A.C.S.[b], Timothy C. Fabian, M.D., F.A.C.S.[c], Wayne K. Langholff, Ph.D.[d], Marsha Wolfson, M.D., F A.C.P.[d]

[a]Department of Surgery, Loyola University Medical Center, 2160 South First Avenue, Maywood, IL 60153, USA; [b]Lehigh Valley Health Network, Allentown, PA, USA; [c]University of Tennessee, Memphis, TN, USA; [d]Janssen Services, LLC, Horsham, PA, USA

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Abstract

BACKGROUND: Achieving a higher hemoglobin (Hb) level might allow the anemic, critically ill, trauma patient to have an improved outcome during rehabilitation therapy.

METHODS: Patients with major blunt trauma orthopedic injuries were administered epoetin alfa or placebo weekly both in hospital and for up to 12 weeks after discharge or until the Hb level was >12.0 g/dL, whichever occurred first. The 36-question Short Form Health Assessment questionnaire (SF-36) was used to evaluate physical function (PF) outcomes at baseline, at hospital discharge, and at several time points posthospital discharge.

RESULTS: One hundred ninety-two patients were enrolled (epoetin alfa [n = 97], placebo [n = 95]). Hb increased from baseline to hospital discharge in both groups (epoetin alfa: 1.2 g/dL vs placebo: 0.9 g/dL), and transfusion requirements were similar between groups. Both groups showed improvements in SF-36 PF; there were no significant differences in the average of all posthospital discharge scores (epoetin alfa: 27.3 vs placebo 30.9; $P = 0.38$). Thromboembolic events were similar between groups.

CONCLUSIONS: No differences were observed in physical function outcomes or safety in anemic, critically ill, trauma patients treated with epoetin alfa compared with placebo.

Anemia is a common problem in critically ill patients. Some etiologies of anemia include sepsis, overt and occult bleeding, decreased production of endogenous erythropoietin because of disease and/or treatments (eg, chemotherapy, renal replacement therapy, use of catecholamines), and immune-related iron deficiency. Consequently, red blood cell (RBC) transfusion is frequently used in critical care settings.[1] Up to 27% of patients in the surgical intensive care unit (ICU) are transfused during their stay.[2] In a United States retrospective study, 85% of ICU patients with stays longer than 1 week were transfused, and the mean number of units of blood transfused per patient was 9.5 units (U).[3] The transfusion of red cells is also known to increase the

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* Corresponding author. Tel.: +1-708-327-2782; fax: +1-708-327-3492.
E-mail address: fluchet@lumc.edu
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risk for immunosuppressive and microcirculatory complications in critically ill patients;[4,5] thus, the use of epoetin alfa as a substitute to transfusions is an appealing alternative in the critical care setting. Epoetin alfa is currently indicated for treating anemia of chronic kidney disease; anemia because of concurrent chemotherapy administration; anemia in zi-dovudine-treated human immunodeficiency virus–infected patients; and for the reduction of allogeneic blood transfusions in elective, noncardiac, nonvascular surgery patients.[6] As an investigational agent, several studies have evaluated the effect of epoetin alfa on transfusion requirements in the critical care setting.[7–9]

Acute anemia, defined as a hemoglobin (Hb) <7 g/dL, is a frequent concern in the critically ill, multiply-injured patient typically managed with additional transfusions after the initial resuscitation for hemorrhage related to injuries.[10] The CRIT Study, by Corwin et al,[11] prospectively evaluated the incidence of anemia, RBC transfusions, and outcomes in 4,892 critically ill patients from 284 ICUs in 213 hospitals across the United States from August 2000 to April 2001. The investigators reported that transfusions were independently associated with longer hospital lengths of stay and an increase in mortality.[11] In a post hoc analysis of this study, the incidence of blood transfusion was more common in the trauma subset of patients when compared with the entire cohort of critically ill patients (55% vs 44%). The trauma patients also received a greater number of blood transfusions (mean, 5.8 ± 5.5 U vs 4.6 ± 4.9 U) when compared with the full study population.[12] A recent prospective, randomized, placebo-controlled trial showed a survival benefit in trauma patients who received epoetin alfa when compared with placebo. Interestingly, there was no transfusion reduction observed with epoetin alfa treatment despite an increase in Hb concentration compared with the control group, suggesting that the mortality benefit was independent of the transfusion effect.[9] In contrast, other studies have shown reduced transfusion needs with epoetin alfa therapy.[7,8]

Orthopedic injuries are a major source of morbidity and mortality in injured patients, particularly when the fractures involve long bones and/or the pelvic girdle, which are associated with major blood loss resulting in acute anemia. As noted earlier, these patients often require additional blood transfusions after the initial resuscitation for shock and control of hemorrhage and are commonly anemic when they enter the rehabilitative phase of care.[13] Recent studies in patients recovering from hip fracture surgery have shown a positive correlation between Hb concentration and functional outcome during the rehabilitation phase. A possible explanation of improved physical activity may be because of an improvement in oxygen delivery.[14,15] The relationship between Hb level and functional outcome during recovery in the multiply-injured patient has not been studied.

This study was conducted to test the hypothesis that achieving a higher Hb level, with epoetin alfa rather than transfusion, might allow the anemic, critically ill, trauma subject to have an improved outcome during rehabilitation therapy. It was hypothesized that the recovery of physical function (PF) would occur earlier in those subjects treated with epoetin alfa compared with those treated with placebo. The primary objective of this trial was to compare the PF outcomes in anemic, critically ill, trauma patients treated with epoetin alfa (Procrit®; Centocor Ortho Biotech Products, LP, Raritan, NJ) or with placebo.

Materials and methods

This study (Protocol PR04-15-001, http://Clinicaltrials.gov: NCT00210626)[16] was a phase 2, prospective, randomized, double-blind, multicenter trial. Subjects were critically ill and had anemia and major orthopedic injuries from blunt trauma. There were 4 consecutive phases: (1) screening (critical care area day 1 up to 6 days [144 hours] before study entry [baseline/study day 1]), (2) in-hospital treatment (first day of study drug treatment through hospital discharge), (3) posthospital discharge treatment (from hospital discharge [week 0] through the last day of week 12 posthospital discharge), and (4) nontreatment follow-up (from the first day of week 13 posthospital discharge through the last day of week 24 posthospital discharge). This study was conducted in accordance with the ethical principles set forth by the Declaration of Helsinki and reviewed by an institutional review board, consistent with good clinical practices. Subjects or their legal representative provided informed consent at screening, after admission to the critical care area, and before study entry.

This was a blinded study, however, in order to optimize acute care, during the in-hospital treatment phase only, study personnel were not blinded to complete blood count or other laboratory results. Epoetin alfa and placebo were administered weekly via subcutaneous injection both in the hospital and for a maximum of 12 weeks posthospital discharge or until Hb level was >12.0 g/dL, whichever occurred first. If Hb was >12.0 g/dL, no further dosing occurred until Hb was < 11.0 g/dL. The study drug was to be administered within a window of ±3 days. Hb was monitored weekly to make dose adjustments. The initial dose of the study drug (or matching placebo) was based on the baseline Hb level, using the following dosing algorithm: (1) if Hb was <9.0 g/dL, then the subject received 40,000 IU; (2) if Hb was 9.0 g/dL to <10.0 g/dL, then the subject received 30,000 IU; (3) if Hb was 10.0 g/dL to < 11.0 g/dL, then the subject received 20,000 IU; and (4) if Hb was 11.0 g/dL to ≤12.0 g/dL, then the subject received 10,000 IU. Assessments of health-related quality of life (HRQOL) were obtained periodically during the study. Laboratory results were monitored for levels of iron, ferritin, transferrin saturation, zinc protoporphyrin, and serum transferrin receptor. Oral iron supplementation was at the discretion of the clinician. Parenteral iron supplementation was not permitted at any time unless specifically allowed by the medical monitor.