

Original Article

Hemoglobin and Hematocrit Rise in End-Stage Renal Disease (ESRD) with PDpoetin: Results of a Phase III, Multicenter Clinical Trial

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ABSTRACT

Background and Objective: The anemia of ESRD is a complex disorder, associated with serious complications, which increases patients' mortality and morbidity. Treatment of this anemia with recombinant human erythropoietin (rHu-EPO) is well established. This clinical trial study was conducted within 20 months, from May 2005 to January 2007, in order to evaluate the efficacy of PDpoetin (rHu-EPO manufactured in Iran) in anemia correction of hemodialysis patients.

Materials and Methods: The study population was composed of 80 patients, aged 22-84 years (with a mean of 49.5 ± 17.5 years), who were 60% male and 40% female. Data were collected by using a questionnaire and a consent form is signed by each patient. All data analysis were carried out using SPSS software and statistical t-test. We administered 50-100 U/kg (up to 300 U/kg in resistant cases) of PDpoetin, 3 times per week, subcutaneously. Then, we followed patients by weekly blood sampling for Hct and Hgb measurement.

Results: PDpoetin raised Hct > 1% and Hgb > 0.3 g/dl per week in 81% and 79% of patients with CRP < 5 mg/dl, respectively. In patients with CRP ≥ 5 mg/dl, these values were 56% and 54%. The mean values of Hct and Hgb rise per week were $1.4 \pm 0.2\%$ and 0.4 ± 0.06 g/dl ($p = 0.0004$ and $p = 0.0002$, respectively), without any statistically significant difference in both gender.

Conclusion: PDpoetin may be an appropriate substitute for commercially available rHu-EPOs (Eprex). Further research studies are recommended.

Key words: Anemia, Erythropoietin, End-Stage Kidney Disease, Hemoglobin

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Introduction

The anemia of renal failure is a complex disorder determined by a variety of factors. Although the primary defect is decreased erythropoiesis due to inadequate erythropoietin (EPO) production from the kidneys, a number of other factors may also play contributory roles (1-3). If untreated, the anemia of chronic kidney disease (CKD) is associated with a number of physiologic abnormalities including decreased tissue oxygen delivery and utilization, cardiovascular complications, impaired host defense and growth retardation in children (4;5).

The cloning and expression of the human EPO was achieved in 1984 (6) and by the end of 1986 the efficacy of recombinant human EPO (rHu-Epo) in reversing the anemia of uremia was established (3;7). EPO is a sialoglycoprotein composed of 165 aminoacids (8), with an estimated molecular mass of 34000 D (9). The carbohydrate moiety, rich in sialic acid, is critical to in vivo reactivity because, asialo form rapidly sequestered in the liver (10).

Renal anemia is rapidly corrected by rh-EPO therapy, but the dose required can vary greatly. Current recommendations are to start with 50 to 100 U/kg (IV) three times per week and therapeutic range is 50-300 U/kg (11).

PDpoetin is a glycoprotein with similar peptide sequence and biological activity but different glycosylation sites. As other commercially available rh-EPOs, PDpoetin is produced in Iran by cloning and expression of EPO cDNA in eukaryotic cell lines of Chinese hamster ovary (CHO). PDpoetin has successfully passed phases I and II of clinical trial. Phase III clinical trial has been performed in this study.

Materials and Methods

This multi- center clinical trial study (phase III) has been conducted as an open study and compared the results of data analysis with previous studies. The required sample size, adjusted based on mean Hgb level of Iranian hemodialysis patients (7.7 g/dl, according to Iranian Dialysis Center report, 1998) and using α and β values of 0.05 and 0.2, respectively, was estimated to be 80 patients. From May 2005 to January 2007, 80 patients were included. The ethical issues of the study involved the assurance of individuals' confidentiality and autonomy for participation. Participants were informed of the

purpose and design of the study and assured that participation was voluntary. The ethical approval was also obtained from the Research Deputy of the Ministry of Health. A consent form is also signed by each patient.

Data were collected by using a questionnaire including age, gender, blood pressure (BP), past medical history [ischemic heart disease, cerebrovascular accident (CVA), malignancies, hypertension (HTN)], C-reactive protein (CRP) (qualitative method), monthly iron parameters (ferritin, serum iron, transferrin saturation «TSAT», basal and weekly hematocrit-hemoglobin (Hct-Hgb) measurements following subcutaneous PDpoetin administration. All data analyses were carried out using SPSS software and statistical t- test.

Patients had to meet the following inclusion criteria: (1) on maintenance hemodialysis at least 3 months, (2) withdrawal from other rh-EPO products at least 6 wks, (3) Hct<30% or Hgb level <10 g/dl, and (4) serum ferritin>100 ng/ml or «TSAT»>20%.

Patients were excluded for any of the following at the beginning of the study: (1) BP \geq 180/110, (2) Hct \geq 30% or Hgb level \geq 10 g/dL, and (3) malignancies, CVA and symptomatic IHD.

Exit criteria after patient enrollment and during the study were seizures, renal transplantation, changing modality of dialysis, established systemic or vascular access infection, vascular access thrombosis, blood transfusion, CVA, uncontrolled hypertension and death.

The study end-point was achieved by patients reaching Hct-Hgb above 33% and 11 g/dL, respectively within any time up to 3 months after PDpoetin administration. We administered 50-100 U/kg of PDpoetin, 3 times per week for all patients subcutaneously. If a patient did not respond to initial dose within 4 wks, the dose doubled. Intravenous iron was prescribed when the ferritin<100 ng/ml or the TSAT was<20%. In these situations, patients received 100 mg of iron intravenously over each of the next 10 hemodialysis sessions and then every 2 wks thereafter. When subsequent iron parameters remained below these values, a repeat loading of 100 mg over the next 5 hemodialysis sessions was given.

Results

Out of 80 patients aged 22-84 years, 60% (48 subjects) were male and 40% female. The mean value of age was 50.07 ± 17.6 years for males and $49.35 \pm$

17.8 years for females.

PDpoetin raised hematocrit greater than 1% and Hgb greater than 0.3g/dl per week in 81% and 79% of patients with $CRP < 5$ mg/dl, respectively. These values in patients with $CRP \geq 5$ mg/dl were 56% for Hct rise and 54% for Hgb. The mean values of hematocrit and Hgb rise per week were $1.4 \pm 0.02\%$ and 0.4 ± 0.06 g/dl (with considering $\alpha = 0.05$, sample size of 80 and $SD = 0.2$ and 0.06 , respectively). The mean value of hematocrit and Hgb rise (3.16 ± 1.12 percent and 1.93 ± 0.71 g/dl, respectively) within 4 wks of PDpoetin therapy were statistically significant ($p = 0.0004$ and $p = 0.0002$; paired t-test, respectively). The mean value of hematocrit and Hgb rise per week was 1.46 ± 0.3 percent and 0.45 ± 0.1 g/dl for males and 1.31 ± 0.18 percent and 0.41 ± 0.06 g/dl for females, respectively. Therefore, PDpoetin-induced hematocrit and Hgb rise did not differ in two genders. Figures 1 and 2 show the mean values of males' and females' Hct and Hgb after PDpoetin administration, respectively.

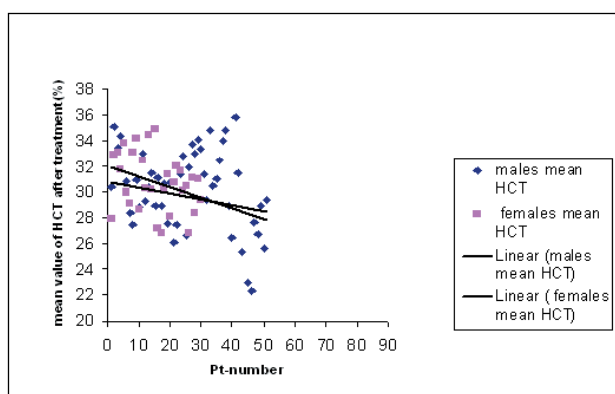


Figure 1: The mean values of Hct for males and females

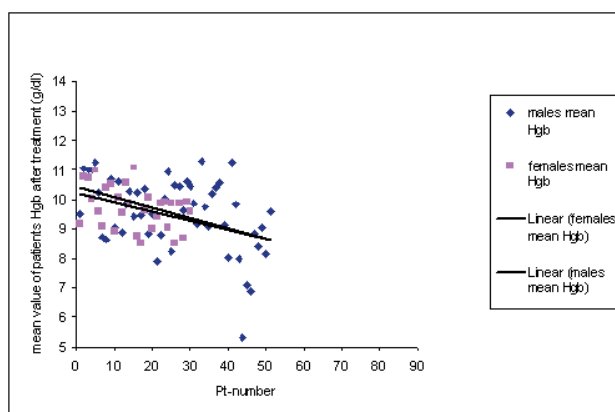


Figure 2: The mean values of Hgb for males and females

Discussion

PDpoetin (Epoetin alfa) is effective in anemia correction of ESRD patients undergoing maintenance hemodialysis without any significant known side-effects including hypertension, clotting, seizures and pure red cell aplasia (6). The mean systolic and diastolic blood pressure alterations after PDpoetin administration were 10 and 2.9 mmHg increment respectively. These alterations are not significant and may be attributed to dietary and hemodynamic improvement following anemia correction. In a review of 47 publications (3428 patients), hypertension was found out in 785 subjects (23%) during rh-EPO treatment (12).

The mean value of hematocrit and Hgb rise per week (above one percent and 0.3 gr/dl respectively) following subcutaneous PDpoetin administration is similar to other studies. In comparison, in one study the rate of Hgb rise was approximately 1 g/dl and 1.5-2 g/dl every 4 wks, for 50 and 100 IU/kg, 3 times per week respectively (11). Winearls et al administered rh-Epo by intravenous bolus to 9 patients 3 times per week and raised the mean Hgb concentration from 6.1 to 10.3 g/dl within 12 wks (13). Eschbach and co-workers administered rh-Epo, intravenously to 25 patients at doses ranging from 15 to 500 IU/kg and demonstrated a dose-dependent response (14). Other clinical trials in the United States, Europe and Japan confirmed these favorable results (15-18). In some studies the subcutaneous administration of EPO appeared more effective and less expensive than the intravenous one (6, 19) requiring on average a 32 % smaller dose to achieve the same target (6;12;19), but this was not confirmed by other study (20). Although both routes of administration are appropriate, we selected subcutaneous route, because we had no experience with PDpoetin administration and its intensity of effect in humans.

Conclusion

In summary, PDpoetin may be as effective as imported rHu-EPOs. Further research studies with larger samples are strongly recommended for PDpoetin efficacy.

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