PDpoietin in Comparison With Eprex in Treatment of Anemic Patients on Hemodialysis

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Introduction. PDpoietin is a recombinant erythropoietin alfa that has been introduced by a manufacturer in Iran. We assessed the effectiveness and complications of PDpoietin in comparison with Eprex in anemic patients on hemodialysis.

Materials and Methods. This clinical trial was performed in a multicenter setting. Patients with a hemoglobin level less than 12 g/dL were assigned into 2 groups in order to receive either Eprex (Janssen Cilag) or PDpoietin (Pooyesh Darou) for 3 months.

Results. Forty-one and 34 patients completed the study in the PDpoietin and Eprex groups, respectively. The mean hemoglobin levels at baseline were not significantly different between the two groups of patients with PDpoietin and Eprex. In both groups, hemoglobin levels increased significantly, but there were no significant differences between the two groups at months 1, 2, and 3. At the end of the study, the mean hemoglobin levels reached 11.6 ± 1.7 g/dL and 11.8 ± 1.9 g/dL, respectively (P = .002; P = .01). The mean hemoglobin per cumulative of drug dose index (hemoglobin/[erythropoietin dose/1000 × injections per month]) was not significantly different between the two groups at different treatment stages, and it did not change significantly in each group during the course of the study. No serious complications were reported.

Conclusions. Eprex and PDpoietin could equally increase the hemoglobin levels with no significant complication. Therefore, PDpoietin can be used for treatment of anemia in patients on dialysis, and the patients will have the advantages of its availability and low price.

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INTRODUCTION

Erythropoietin is a hormone made by the kidney precursor cells and is effective in the production of erythrocytes. Erythropoietin is also locally produced by other tissues in response to metabolic and physiologic stresses.[1-5] Concerning the exogenous administration of erythropoietin, correction of anemia by this hormone improves hypoxia and reduces oxygen free radicals.[4]

In patients with end-stage renal disease, the natural production of erythropoietin by the kidneys is impaired, and therefore, replacement by exogenous erythropoietin is required. The dosage of erythropoietin, however, is changeable; depending on the hemoglobin level, the physician increases the dose or holds its injection. The available

erythropoietin in the market has a concentration of 2000 U/mL, 4000 U/mL, or 10 000 U/mL, that is usually injected 3 times per week for patients on maintenance dialysis. There are 2 types of erythropoietin alfa and erythropoietin beta. The alfa type of erythropoietin is usually used for treatment of anemia.

Some brands of generic or nongeneric types of recombinant human erythropoietin are used in Iran, including Eprex (Janssen Cilag, Beerse, Belgium) and PDpoietin (Pooyesh Darou, Tehran, Iran). PDpoietin is a recombinant human erythropoietin alfa that has been introduced by a manufacturer inside the country. Thus, it can be much affordable and available for the Iranian patients. On the other hand, Eprex is associated with some known complications such as hypertension, headache, flue-like syndrome (hypersensitivity reaction), and irritation, pain in the injection site.[6] Therefore, PDpoietin can be an alternative in patients who experience these complication. Moreover, a series of etiologic factors can lead to erythropoietin resistance, including iron deficiency anemia, chronic inflammation, occult malignancies, aluminum intoxication, severe hyperthyroidism, and malnutrition.[5,6] These condition may necessitate attempting other available types of the drug. In the present study, we assessed the effectiveness and complications of PDpoietin in comparison with Eprex in anemic patients on hemodialysis.

MATERIALS AND METHODS

This multicenter clinical trial was performed from June to August 2007 on the patients who were receiving long-term hemodialysis at 5 centers in Tehran, Iran (Shahid Labbafinejad, Shahid Hasheminejad, Shahid Modarres, Dr Shariati, and the Red Crescent hospitals). The inclusion criteria were being on hemodialysis for at least 3 months, age between 15 and 80 years, hemoglobin level less than 12 g/dL at the time of enrollment (regardless of receiving treatment by erythropoietin or not). Patients with any of the following conditions were not selected for the study: malnutrition, malignancy, chronic inflammation, any history of hospitalization in the past 3 months, positive C-reactive protein test, and serum parathormone level higher than 1000 pg/mL. In addition, erythropoietin-resistant patients who needed blood transfusion, those who underwent kidney transplantation during the study period, AND noncompliant patients were excluded from the study. Eligible patients provided informed consent to be enrolled in the study. Pooyesh Darou company was the financial supporter of the study, and the Iranian Society of Nephrology supervised the project and supplied the dialysis centers with the erythropoietin products.

Due to ethical considerations, no washing period was considered for starting the study and none of the previously being administered drugs were changed. The patients were divided into 2 groups to receive either PDpoietin (Pooyesh Darou, Tehran, Iran) or Eprex (Janssen Cilag, Beerse, Belgium) for treatment of anemia, regardless of which type of the drug they were receiving. At each dialysis center, 20 patients were recruited and randomly divided into the two groups. Eprex and PDpoietin were subcutaneously administered after each session of dialysis for 3 months, and their dosages were adjusted to achieve a hemoglobin level of 12 g/dL or hematocrit level between 33% and 36%. In case of a hemoglobin level exceeding to 12 g/dL, erythropoietin was discontinued and after each change, the physician decided on erythropoietin dosage. Hemoglobin and hematocrit levels were assessed every 1 month during the study period. One nurse at each dialysis center was responsible to prepare covered syringes for injection in order to make the researcher and the patients blind to the type of erythropoietin. The patients also received folic acid, 5 mg/d, and vitamin B12, 100 µg/w, in order to eliminate other causes of anemia. If iron deficiency was diagnosed on monthly laboratory examinations (serum ferritin < 100 µg/L, and transferrin saturation < 20%), saccharated ferric oxide was also administered (100 mg once to 3 times per week).

All laboratory examinations were performed at baseline and months 1, 2, and 3 of the study. Complications or side effects of the drugs were recorded, and hypotension, coagulopathy, immune reactions, pain on the injection site, and serum electrolyte disorders were specifically considered during the study. Changes in the diet of the patients were checked by monthly interviews with nutritional queries listed in Table 1. Our criteria for detection of malnutrition were the albumin index (hypoalbuminemia), body mass index and subjective and objective items including weight loss and anorexia. Finally, an index of hemoglobin/

Table 1. Questions on Diet Habit Changes

Interview Questions
1. Did you have new food habit?
2. Did you change the amount of meat compared to the last month?
3. Did you change the amount of cereals meat compared to the last month?
4. How many times did you go to your family's home for eating?
5. In general, did you have any changes in your food habit that was important for you?

cumulative of drug dose was defined to assess the effect of erythropoietin in relation to hemoglobin changes, using the following formula:

Hemoglobin level/(erythropoietin dose/1000 × injection times per months)

The higher was the index, the better was the response to the medication.

Data were analyzed using the SPSS software (Statistical Package for the Social Sciences, version 13.0, SPSS Inc, Chicago, Ill, USA). Comparisons between the two groups were done by the *t* test and the chi-square test, where appropriate. Hemoglobin levels at different stages of the study were compared in each group using the paired *t* test. A *P* value less than .05 was considered significant.

RESULTS

Twenty patients at each 5 dialysis center were enrolled. However, 9 patients in the PDpoietin group and 16 in the Eprex group were excluded according to the study's established criteria. Therefore, 41 and 34 patients completed the study in the PDpoietin and Eprex groups, respectively. Demographic and clinical characteristics of the patients at baseline are listed in Table 2. The patients with PDpoietin were older than those on Eprex ($P = .02$).

The mean hemoglobin levels at baseline were not significantly different between the two groups of patients with PDpoietin and Eprex (10.1 ± 2.0 g/dL versus 10.5 ± 2.0 g/dL; $P = .38$). In both groups, hemoglobin levels increased significantly, but there were no significant differences between the two groups at months 1, 2, and 3 (Table 3). At the end of the study (3rd month), the mean hemoglobin levels reached 11.6 ± 1.7 g/dL and 11.8 ± 1.9 g/dL in patients with PDpoietin and Eprex, respectively ($P = .002$; $P = .01$). It is noteworthy that hemoglobin levels did not have a significant increase from month 2 and month 3 in neither of the groups, while the increasing trends from month 1 to month 2 were significant for both groups.

After 1 month, 10 patients (24.4%) in the PDpoietin group and 14 (41.2%) in the Eprex group reached target hemoglobin level. After the 2nd month, 20 (47.8%) and 16 (47.0%) had a hemoglobin level higher than 12 g/dL, respectively. Finally, after 3 months, 21 (51.2%) and 17 (47.0%) in the PDpoietin and Eprex groups had the favorable hemoglobin level ($P = .91$). The mean hemoglobin per cumulative of drug dose index was not significantly different between the two groups at different treatment stages (Table 4), and it did not changes significantly in each group during the course of the study.

In the PDpoietin group, 11 patients (26.8%) reported to be generally better than before after 3 months, in comparison with 3 (8.8%) in the Eprex group. Regarding nutritional status, 24 (58.5%)

Table 3. Hemoglobin Levels of Patients on Hemodialysis During the Study

Time of Treatment	PDpoietin Group	Eprex Group	*P*
Baseline	10.1 ± 2.0	10.5 ± 2.0	.38
Month 1	10.9 ± 1.9	11.1 ± 1.9	.58
Month 2	11.4 ± 1.8	11.7 ± 1.6	.43
Month 3	11.6 ± 1.7	11.8 ± 1.9	.71

Table 2. Baseline Demographic and Clinical Characteristics of Patients on Hemodialysis

Characteristics	PDpoietin Group	Eprex Group	*P*
Age, y	51.7 ± 16.0	43.4±19.3	.02
Sex			
Male	27	19	
Female	14	15	.39
Hemoglobin, g/dL	10.1 ± 2.0	10.5 ± 2.0	.22
Serum ferritin, µg/L	501.3 ± 309.1	630.0 ± 411.0	.13
Total iron binding capacity, µg/dL	270 ± 66	268 ± 64	.56
Serum iron, µg/dL	70.48 ± 32.09	71.84 ± 26.40	.33
Serum parathyroid hormone, pg/mL	248.8 ± 233.0	296.2 ± 249.6	.15

Table 4. Mean Hemoglobin per Cumulative of Drug Dose Index in Patients on Hemodialysis*

Study Period	Hemoglobin per Cumulative of Drug Dose Index		
	PDpoietin Group	Eprex Group	*P*
Baseline	0.51	0.63	.21
Month 1	0.54	0.52	.84
Month 2	0.58	0.54	.74
Month 3	0.57	0.55	.86

*The index was calculated as hemoglobin/(erythropoietin dose/1000 × injections per month)

and 29 (85.3%) patients in the PDpoietin and Eprex groups believed that they experienced no significant changes (Table 5). Complications seen in the patients are listed in Table 7. Thirty-nine patients (95.1%) in the PDpoietin group and 33 (97.1%) in the Eprex group had an uneventful study period without any side effects (Table 6).

Table 5. Changes in Nutritional Status of Patients on Hemodialysis and Erythropoietin After 3 Months of Treatment*

Nutritional Status	PDpoietin Group	Eprex Group
Without change	24 (58.5)	29 (85.3)
Better than before	11 (26.8)	3 (8.8)
Worse than before	6 (14.6)	2 (5.9)

*Values in parentheses are percents.

Table 6. Complications and Side Effects in Patients on Hemodialysis and Erythropoietin

Complication	PDpoietin Group	Eprex Group
Local pain	1 (2.4)	0
Hypertension	1 (2.4)	0
Immunologic reaction	0	1 (2.9)
Need for blood transfusion	0	0

DISCUSSION

The cause of anemia in patients with chronic kidney disease and those on dialysis is the reduction in the production of erythrocytes which in turn is due to the impaired ability of the kidneys to secrete erythropoietin. The beneficial effect of dialysis on the uremic complications depends on the nature of the complications; erythrocyte production slightly improves by the start of dialysis which is probably due to the reduction in the level of uremic toxins; however, dialysis cannot completely substitute the functions of the kidneys, and therefore, erythropoietin production would not be sufficient yet. On the other hand, uremic toxins and accumulation of aluminum in patients on dialysis affect the bone marrow and further impair their erythrocyte production.[2]

Treatment of anemia in patients on dialysis has changed a lot during the recent years. Previously, these patients were treated by blood transfusion and injection of testosterone. In massive transfusion, however, some serious complication including iron overload, antibody formation, and viral infections can develop. In addition, testosterone was not quite beneficial in the treatment of such patients and virilization was a very important side effect in women.[2] In 1983, the erythropoietin gene was detected and used for production of erythropoietin in order to be used in patients with chronic kidney disease.[2] Increased hematocrit level in these patients has increased the tolerance of the patients to activities and the sense of well-being. However, high price of this medication is a factor affecting the policies of the insurance corporations.[2] Another most important item in the treatment of these patients is that if the iron reserve is not enough, the response to the treatment will not be sufficient.

Availability of the recombinant erythropoietin has been a revolutionary change in the treatment of anemic patients. The dosage of erythropoietin is different among the patients depending on the degree of iron sufficiency. After initialization of the treatment, it takes 1 to 2 months for the patient to feel better. Of the erythropoietin side effects is flu-like syndrome which presents with myalgia about 60 to 90 minutes after the intravenous injection of the drug. It is not generally a serious side effect and will diminish after the continuous use of the hormone. Also, increase in the level of hematocrit may cause hypertension (in one-third of the patients with a hematocrit higher than 30%).[5-7] In a study in 2004, the results of iron-deficiency anemia in 11 041 patients on dialysis were evaluated. Erythropoietin was generally administered in conjugation with calcium and evaluation of the iron profile. It was obvious by the end of the study that all internationally

accepted methods caused significant increase in the hemoglobin level and control of anemia.[8] In another study, 2618 patients were evaluated in 6 months. Generally, the treatment started when the hemoglobin level was very low. However, complete regular monitoring could significantly improve the patients' outcome.[9]

In a study done in 2005, treatment with recombinant erythropoietin was evaluated. The researchers noted no significant differences were in the results when recombinant erythropoietin was used 1, 2, or 3 times per week. Therefore, the mediation can be administered once a week or more according to the tolerance of the patient.[10] Other factors affecting the response to the treatment by erythropoietin have been evaluated, as well. Calcitriol has been effective in improvement of anemia and reduction in the dose of erythropoietin.[11,12] Also, the effect of intravenous injection of vitamin C in patients on hemodialysis with resistant anemia and high ferritin levels has increased the response to erythropoietin, which seems to be due to the antioxidant effect of vitamin C.[13] The use of iron can also increase response to erythropoietin and reduce the its needed dose.[14] We used two erythropoietin products in our patients and prepared similar conditions in the two groups by correcting iron deficiency and administering vitamin B 12, folic acid, and iron supplement. PDpoietin was as effective as the widely used Eprex.

CONCLUSIONS

We showed that in patients on hemodialysis, Eprex and PDpoietin both increased the level of hemoglobin, and thus improved anemia and changed nutrition status to a better state. Hemoglobin changes were significant in both groups of PDpoietin and Eprex. There were not any significant side effects in the two groups. We conclude that we can use PDpoietin for treatment of anemia in patients on dialysis, as it has good efficacy and is cost benefit, and is locally available.

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CONFLICT OF INTEREST

This study was proposed by Pooyesh Darou company to the Iranian Society of Nephrology, and the researchers were supported by the budget and drug supply distributed by the Iranian Society of Nephrology as the mediator and supervisor of the project.

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