Multicenter Trial of Erythropoietin in Patients on Peritoneal Dialysis[1]

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ABSTRACT

A randomized, double-blind, placebo-controlled, multicenter trial was performed to assess the safety and efficacy of subcutaneous recombinant erythropoietin (EPO) in peritoneal dialysis patients. Seventy-eight patients were randomized to receive EPO and 74 received placebo during the first 12 wk. After this, placebo patients with hematocrit less than 32% entered the EPO maintenance phase along with the initial EPO patients. Hematocrit rose significantly in the EPO group from 23.8 to 32% after 6 wk, and this was sustained at 33.7% at 12 wk. In the placebo group, the prestudy hematocrit was 23.8% as well, and no significant change in hematocrit occurred over 12 wk. Concomitant with the rise in hematocrit, transfusion requirements fell only in the EPO group. Eighty-eight percent of patients receiving EPO had their anemia ameliorated by Week 12 of the study. There was a wide range of dosage requirements during the maintenance phase, ranging from 8,000 U thrice weekly to 4,000 U every other week. Adverse events after EPO were similar to those seen in hemodialysis patients given this agent, with hypertension developing or worsening in 55% of EPO patients during the initial 12 wk of therapy. Blood pressure was more likely to rise in patients with hypertension before receiving EPO. EPO is safe and effective in peritoneal dialysis patients, as it is in hemodialysis patients. Other than a rise in blood pressure, which is manageable with antihypertensives and ultrafiltration with dialysis, no serious side effects are seen. The optimal target hematocrit, effects of anemia improvement on quality of life, and end-organ (heart, brain) effects of anemia improvement in this patient population require further study.

Key Words: *Hypertension, renal anemia, peritoneal dialysis, dialysis, iron*

Patients undergoing peritoneal dialysis (PD) have less severe anemia than do those receiving hemodialysis (HD) (1–4). This has been attributed in part to hemoconcentration caused by the continual fluid removal achieved with PD (5,6). On the other hand, an increase in red blood cell mass has been found by some investigators (5–9). Chandra *et al.* found significantly higher EPO levels in PD compared with HD patients (10). Reasons proposed for this finding include extrarenal EPO production by activated peritoneal macrophages, removal of uremic inhibitors of EPO production, blood loss associated with the HD procedure, and generally improved protein metabolism. Others have speculated that the enhanced removal of middle-molecular-weight toxins by PD compared with HD accounts for an increase in red blood cell survival and a more robust bone marrow response to EPO in the former with a resultant higher hematocrit (9,11–13). Whatever the mechanism of the higher ambient hematocrit seen in PD compared with HD patients, it is of clinical significance. Blood transfusions were used far less frequently in PD compared with HD patients in the pre-EPO era (2,14,15). In addition, fewer PD patients compared with HD patients are being treated with EPO (2,16). Numerous studies have been published that assess the response of PD patients to EPO given iv, sc, or ip (17–25). In general, the results are similar to those seen in HD patients given EPO iv or sc, with a favorable response

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in the majority of patients. These previous studies suffer, however, from small patient numbers, single-center design, and lack of placebo controls. This study was carefully developed to avoid these shortcomings by evaluating the safety and efficacy of EPO in a large number of PD patients using a multicenter, placebo-controlled design.

PATIENTS AND METHODS

Study Overview

This randomized, double-blind, placebo-controlled, multicenter clinical trial was designed to evaluate the efficacy and safety of self-administered EPO in PD patients. Patients fulfilling the study requirements were enrolled and randomized in equal numbers to receive either EPO (Group I) or placebo (Group II) during the first 12 wk of the study. The frequency of administration of the study medication was decreased for the remainder of the 12-wk period if the hematocrit increased to between 32 and 38%. After 12 wk, the study was unblinded, and all patients were evaluated for eligibility to enter the long-term maintenance phase of the trial. Patients who had received EPO during the blinded phase were eligible to continue in the trial and receive EPO only if they had achieved a hematocrit of more than 32%, or an increase of at least 10 percentage points from the baseline hematocrit. Patients who had received placebo and still maintained a hematocrit of less than 32% were managed on EPO for the next 12 wk according to the same protocol and then evaluated for long-term maintenance by the same criteria as those initially receiving EPO. In addition to studying efficacy and safety, an additional goal of the long-term maintenance phase was to determine the minimal frequency of EPO dosing that would maintain the target hematocrit of 32 to 38%.

Patient Selection Criteria

Inclusion Criteria. Patients were eligible for initial entry into the study if they met all of the following criteria: diagnosis of ESRD and undergoing chronic PD daily for at least 3 months before enrollment; receiving medical supervision by the investigator for at least 1 month; clinically stable as judged by the investigator, on the basis of documented patient history; male gender or if female using contraceptives or judged unable to become pregnant; age older than 18 yr; ambulatory; baseline hematocrit less than 30%; serum ferritin greater than 100 ng/mL and transferrin saturation greater than 20%; aspartate aminotransferase not exceeding twice the upper limit of normal.

Patients who had received placebo during the blinded phase still had to have a hematocrit less than 32% before receiving open-label EPO. To enter the long-term maintenance phase, all patients (Groups I and II) had to have achieved a hematocrit of more than 32% or at least 10 percentage points greater than the baseline hematocrit while receiving EPO.

Exclusion Criteria. Patients were excluded for any of the following reasons: systemic hematologic disease that would interfere with the evaluation and interpretation of the data (*e.g.*, sickle cell anemia, thalassemia, myelodysplastic syndromes, or hematologic malignancies); more than one documented episode of peritonitis within the past 4 months or clinical evidence of peritonitis within the past 30 days; likelihood of receiving a kidney transplant within the first 90 days on-study; current drug addiction; consistent supine diastolic blood pressure of 100 mm Hg or higher; thrombocytopenia (platelet count less than 100,000/mm^3); hemolytic anemia, Coombs positive or negative; participation in any other clinical investigational drug or biologic study while participating in this study or within the past 30 days (including, but not limited to, antihypertensive and antibiotic studies); androgen therapy initiated in the preceding 4 wk or changes in dose of androgens in the preceding 4 wk; desferoxamine therapy during the prestudy period; uncontrolled seizure disorder.

Study Medication

Dose, Route of Administration, and Schedule. Study medication was self-administered sc thrice weekly at approximately the same time of day, with a standardized rotation schedule of at least four sites. At each administration, the dose administered (1.0 mL), the lot number, the site of administration, and any adverse events were recorded in the patient diary. During the blinded phase, this consisted of placebo or EPO at 4,000 U/mL. In the maintenance phase, the EPO dose was titrated, as described below, with the use of 2,000, 4000, or 10,000 U/mL concentrations. Missed doses were not made up; if a patient missed a scheduled dose of study medication, the dose allotted for that day was not administered the following day.

Dose Modification During the Double-Blind Phase. If a hematocrit of 32 to 38% was reached within the first 12 wk of the study, the frequency of study medication administration was reduced to twice weekly (*e.g.*, Monday, Friday). Dose frequency was subsequently reduced to once weekly and then less frequently as required to maintain a hematocrit of 32 to 38%. If a hematocrit increased above 38%, doses of study medication were withheld until the hematocrit decreased to 35%, at which time, treatment was resumed at the reduced frequency specified above.

Dose Modification During the Long-Term Maintenance Phase. Patients who had received EPO during the randomized, double-blind, placebo-controlled phase, or who had received placebo and subsequently crossed over to receive EPO at a dose of 4,000 U per administration, and attained the target hematocrit range, were eligible for the long-term maintenance phase. The goal of the long-term maintenance phase was to reduce the frequency of EPO dosing to the minimal number of administrations per week that would maintain the target hematocrit range of 32 to 38%.

Description of Placebo. The placebo used in this study contained only the excipient (0.25% albumin [human] in sterile buffered saline). Like EPO, the placebo was nonpyrogenic and was a sterile, clear, colorless, particle-free solution.

Study Evaluations

Randomization. All study materials were labeled identically except for the patient number. The randomization sequence was designed to ensure that approximately equal numbers of patients were randomized to either EPO or placebo. At each center, treatment unit numbers were assigned consecutively by date of randomization. Each center had a unique randomization schedule with a block size of four.

Double-Blind Phase. Patients reported to the dialysis center at specified intervals for testing. During the first 12 wk on-study, the evaluations were performed at weekly or biweekly intervals. An uncontrolled supine diastolic pressure of higher than 100 mm Hg was an exclusion criterion. Blood

pressure was carefully monitored during the study, and antihypertensive medication was initiated or increased when necessary. Blood pressure and any adverse events were recorded daily by the patient in the patient diary. Concomitant therapy, transfusions, hospitalizations (reason and duration), changes in dialysis prescription, and other clinical observations were recorded at least weekly on the Case Report Form. At the end of the 12-wk double-blind phase, each patient underwent a complete physical examination. Chest radiographs (posteroanterior and lateral) and an electrocardiogram were obtained, if medically indicated. A coagulation screen (prothrombin time and partial thromboplastin time) was performed. All laboratory determinations (including complete blood count, reticulocyte count, iron studies, and biochemistry), scheduled on a biweekly, weekly, semimonthly, or monthly basis, were performed. Quality of life was also assessed and will be reported in a subsequent publication.

Long-Term Maintenance Phase. After the first 12-wk treatment with EPO, the schedule of evaluations was modified for the long-term maintenance phase but still required weekly evaluation of blood pressure, complete blood count, and reticulocyte count and monthly assessment of biochemistry and iron status.

Assessment of Efficacy and Safety

The primary efficacy variables of the short-term portion of this study were hematocrit and red blood cell transfusion requirements. Secondary efficacy variables were quality of life and the rate and percentage of patients reaching the target hematocrit. Between-group comparisons were made for these variables with data from the double-blind phase.

An increase in hematocrit to 35% or six percentage points higher than the baseline hematocrit was considered a positive clinical response from which all patients would be expected to benefit. Even for those patients whose hematocrit increased by less than six percentage points, EPO therapy was considered of significant medical benefit if transfusion requirements were eliminated or decreased. During the maintenance phase, the primary efficacy variables were successful maintenance of hematocrit within the target range and determination of the minimal effective dose. The endpoints for safety assessment were adverse events, blood pressure, and laboratory data.

Analytical Methods

All analyses were performed with the SAS-PC, version 6.04. Laboratory and clinical data were collected before treatment to provided baseline values to which the results of similar on-study observations and determinations could be compared. The intent-to-treat principle was used for all analyses.

Analysis of Efficacy Data. To determine the efficacy of EPO in ameliorating ESRD anemia, each patient's response (*i.e.*, increase in hematocrit) was evaluated. Because the rate at which a patient responded to EPO therapy was likely a function of many different parameters (including vitamin and iron status, presence of infection, and EPO dose), patients were expected to respond at differing rates. Transfusion requirements and the rate and extent of anemia amelioration were also evaluated. Dose data for patients who were stabilized on EPO were evaluated to determine dose requirements.

Analysis of Safety Data. Adverse events were tabulated. Event counts and patient counts of all adverse events were tabulated in three 6 × 6 cell grids (EPO group [blinded phase], placebo group [blinded phase], and all EPO administration during the study), which display the event and patient counts by grade of severity and relation to study medication. Adverse events and selected clinically significant adverse events were tabulated for the blinded phase and for the period including all EPO administrations during the study. Events leading to hospitalization during the blinded phase were tabulated.

Statistical Methods: General Approach

For this analysis, a significant P value was less than 0.05. Type III sums of squares were used for all analyses involving linear models (PROCGLM). Centers 03, 07, 15, 16, and 18 were combined and called Center 99 for analysis purposes, because these centers had fewer patients than any others. Because the study consisted of a 12-wk blinded phase and an open-label, long-term maintenance phase, blood pressure and laboratory data from the double-blind phase only were used for the statistical analysis of the efficacy. The Kruskal-Wallis test, a generalization of the Mann-Whitney test, was used for between-group comparisons. The analysis of variance (ANOVA), a generalization of the unpaired t test, was used for analysis of baseline data; the analysis of covariance was used for subsequent analysis. Because there were only two treatment groups, the Kruskal-Wallis test reduced to the Mann-Whitney, and the ANOVA reduced to the unpaired t test.

RESULTS

Investigators and Sites

Principal investigators at 16 study sites contributed patients to this study. The names of the investigators and the study sites are listed in the Appendix.

Patient Accrual and Duration of Treatment

The first patient received study medication on September 27, 1989. The last patient's final data were recorded on January 10, 1992. Table 1 accounts for all patients accrued on-study and lists the reasons why patients were removed from the study. Of the 152 accrued patients, 78 (51%) were randomized to EPO and 74 (49%) were randomized to placebo. Of the 152 randomized patients, 136 (89%) completed the blinded phase of the study. All 136 patients subse-

TABLE 1. Patient accrual and reasons for dropouts

No. of Patients	Blinded		Maintenance EPO
	EPO	Placebo	
Accrued	78	74	136[a]
Completed	69	67	76
Dropped Out	9	7	60
Reason for Dropout			
Kidney transplant	3	1	17
Change to HD	0	0	15
Death	2	1	8
Adverse event	2	1	6
Other	2	4	14

[a] All 136 patients who completed the blinded phase entered the maintenance phase.

quently enrolled in the open-label, long-term maintenance phase. Sixteen patients (11%) dropped out during the blinded phase, and 60 patients (44%) dropped out during the maintenance phase. In total, 76 patients were removed from the study for the following reasons: kidney transplant ($N = 21$), change to HD ($N = 15$), death ($N = 11$), adverse event ($N = 9$), and other reasons ($N = 20$). Patients who developed peritonitis during the study remained in the study. Sixteen patients dropped out of the study during the blinded phase (nine EPO, seven placebo). Of the 60 patients who were removed during the maintenance phase, 29 had been randomized to EPO and 31 had been randomized to placebo.

Patient Characteristics

Characteristics for all patients, presented in Table 2, were similar between treatment groups. Table 3 summarizes the primary cause of ESRD for patients enrolled in this study.

Comparison of the Study Population to the General PD Population

Table 4 compares the gender distribution, age, and primary cause of ESRD of the PD patients in this study and the PD patients described in the 1992 United States Renal Data System (USRDS) report. Gender ($P = 0.001$) and primary cause of ESRD ($P < 0.0005$) of the study population differed significantly

TABLE 2. Patient characteristics

Characteristic	EPO ($N = 78$)	Placebo ($N = 74$)	P
Age (yr)			
Mean ± SD	46.8 ± 15.5	49.9 ± 15.9	0.32[a]
Median	46.5	49.0	
Range	19.0–78.0	19.0–87.0	
Weight (kg)			
Mean ± SD	71.7 ± 17.8	70.8 ± 18.0	0.86[a]
Median	69.0	69.2	
Range	43.5–123.0	39.1–117.0	
Height (cm)[b]			
Mean ± SD	165.5 ± 11.5	165.2 ± 10.8	0.71[a]
Median	167.0	165.0	
Range	130.9–195.6	148.0–185.0	
Time on Dialysis (yr)			
Mean ± SD	3.5 ± 4.8	3.1 ± 3.2	0.48[a]
Median	1.6	2.0	
Range	0.2–23.7	0.3–16.4	
Time On-Study (wk)			
Mean ± SD	48.6 ± 26.0	54.0 ± 27.8	0.42[a]
Median	48.6	59.0	
Range	1.3–98.0	2.3–98.0	
Time Since Renal Failure (yr)			
Mean ± SD	6.6 ± 7.3	6.4 ± 5.7	0.72[a]
Median	3.5	4.6	
Range	0.3–32.0	0.3–25.8	
Gender			
Male	31 40	28 38	0.77[c]
Female	47 60	46 62	
History of Hypertension			
Yes	67 86	68 92	0.25[c]
No	11 14	6 8	
Current Hypertension			
Yes	44 56	41 55	0.96[c]
No	34 44	33 45	
History of Diabetes Mellitus			
Yes	21 27	18 24	0.75[c]
No	57 73	56 76	

[a] Two-way ANOVA with center, treatment, and interaction.
[b] In the EPO group, baseline height was reported for only 77 patients.
[c] Cochran-Mantel-Haenszel test of nonzero correlation.

TABLE 3. Primary cause of ESRD[a]

Disease Category	EPO (N = 78)		Placebo (N = 74)	
	N	%	N	%
Diabetic Nephropathy	19	24	12	16
Hypertension	19	24	23	31
Glomerulonephritis	18	23	14	19
Polycystic Kidney Disease	4	5	4	5
Other	18	23	21	28
Total	78	100	74	100

[a] The Cochran-Mantel-Haenszel test of nonzero correlation gives $P = 0.15$.

from those of the general PD population. Many but not all of the between-group differences in primary cause of ESRD were explained by the fewer numbers of patients in the study population with unreported or unknown causes. Even without that category, the difference was still significant ($P = 0.02$). Although the USRDS provides patient counts for various age ranges rather than mean age data, the approximate mean age of the general PD population in 1989 was 52 yr, which is older than the mean age of the study population (48 yr).

Selected Concomitant Therapy: Blinded Phase

Because angiotensin-converting enzyme (ACE) inhibitors may inhibit erythropoiesis in some patients, aluminum toxicity can cause microcytic anemia and EPO resistance, and nonsteroidal anti-inflammatory drugs (NSAID) and aspirin can cause gastrointestinal blood loss, the use of antihypertensives, phosphate binders, and NSAID and aspirin was compared between treatment groups. The distribution of the selected concomitant therapies between treatment groups was similar. Ninety-six patients (63%) received antihypertensive medications: 52 (34%) received calcium channel blockers, 40 (26%) received ACE inhibitors, 33 (22%) received β-blockers, 23 (15%) received antiadrenergics, and 21 (14%) received vasodilators. Of the 40 patients (26%) who received ACE inhibitors, 11 (28%) were diabetic. Non-aluminum-containing phosphate binders were taken by 74 patients (49%). NSAID, including aspirin-containing medications, were taken by 32 patients (21%).

Iron Administration

At baseline, iron parameters were identical in the EPO and placebo groups. Sixty-one patients (40%) received parenteral iron during the study. Eight patient (5%) required parenteral iron to enter the study, 28 patients (18%) required parenteral iron during the blinded phase, and 51 patients (38%) required parenteral iron during the maintenance phase. At study entry and during the maintenance phase, parenteral iron requirements were comparable between groups; however, during the blinded phase, significantly ($P < 0.0005$) more EPO patients ($N = 23$) required parenteral iron compared with placebo patients ($N = 5$). One hundred thirty-two patients (86%) received oral iron (ferrous fumarate, ferrous gluconate or ferrous sulfate) during the study. During the blinded phase, more EPO patients required oral iron than did placebo patients, whereas during the maintenance phase, iron requirements were comparable between groups.

Hematologic Response

As seen in Table 5 and Figure 1, the mean baseline hematocrit was identical for each treatment group. By Week 6, the mean hematocrit was significantly higher

TABLE 4. Comparison of the study population to the U.S. PD Population

Characteristics	Study Population (N = 152) %	U.S. PD Population[a] (N = 14,150) %	P
Gender			
Male	39	52	0.001[b,c]
Female	61	48	
Age (yr)	48	52[d]	
Primary Cause of ESRD			
Diabetes	20	26	<0.0005[b], 0.02[e]
Glomerulonephritis	21	21	
Hypertension	28	21	
Polycystic Kidney	5	5	
Other urologic	11	6	
Other	12	7	
Unreported/unknown	2	14	

[a] Year-end percentages from the 1992 USRDS data report.
[b] The χ^2 approximation to the likelihood ratio test.
[c] The normal approximation to the binomial test without continuity correction.
[d] Approximate mean age.
[e] The χ^2 approximation to the likelihood ratio test without the unreported/unknown category.

TABLE 5. Hematocrit response during the blinded phase

Study Period	EPO		Placebo		P[a]
	N	Hematocrit (%) + SD	N	Hematocrit (%) + SD	
Baseline	78	23.8 ± 3.8	74	23.8 ± 3.3	0.96
Week 6	74	32.0 ± 4.4	69	25.1 ± 3.6	0.01
Week 12	68	33.7 ± 4.8	64	24.1 ± 3.8	0.01

[a] ANOVA (center, treatment and interaction) at baseline and analysis of covariance (center, baseline, treatment and center × treatment) subsequently.

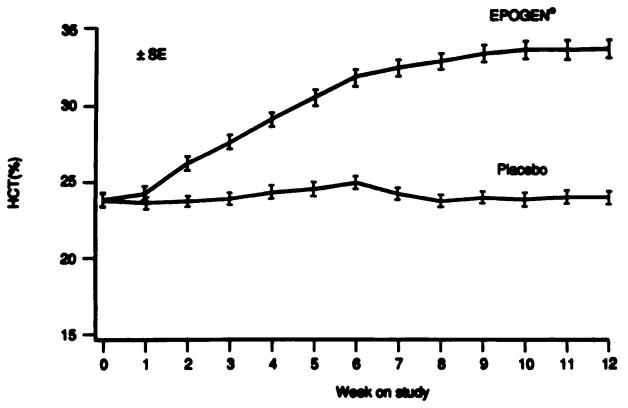

Figure 1. Hematocrit (Hct) response to EPO or placebo in PD patients.

in the EPO group (32.0 versus 25.1%; $P = 0.01$). The difference was sustained at Week 12 (33.7 versus 24.1%; $P = 0.01$).

Within-group differences were compared with the Wilcoxon signed-ranks test and the paired t test. For the EPO group, the mean hematocrit was significantly higher at 6 (23.8 versus 32.0%; $P = 0.0001$) and 12 wk (23.5 versus 33.7%; $P = 0.0001$). For the placebo group, the mean hematocrit was significantly higher at 6 (23.8 versus 25.1%; $P = 0.004$, paired t test) but

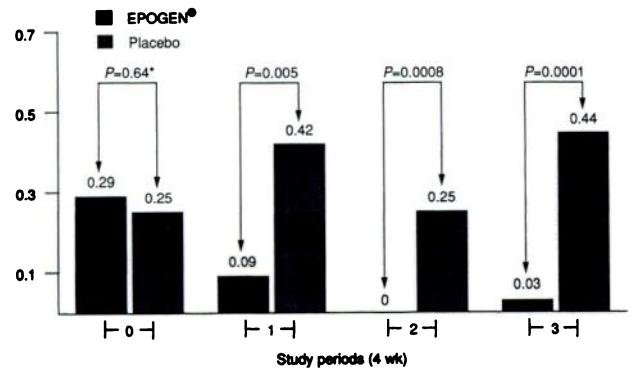

Figure 2. Transfusion requirements in PD patients on EPO or placebo.

not at 12 weeks. The increase in the hematocrit of the placebo group is most likely the result of concomitant transfusions (Figure 2). As expected, the increases in red blood cell count ($P = 0.0001$) and hemoglobin ($P = 0.0001$) observed in the EPO group were of similar magnitude.

Red Blood Cell Transfusions

During the 6 months before the study, the mean number of red blood cell units transfused per 4 wk did not differ significantly between groups (0.29 ± 0.05 U/patient per 4 wk for EPO patients and 0.25 ± 0.05 U/patient per 4 wk for placebo patients, $P = 0.64$). During the 12-wk blinded phase, transfusion data were divided into three 4-wk periods. Those data were subjected to within-group and between-group statistical analyses. As shown in Table 6, the transfusion requirements of EPO patients decreased significantly to an average of 0.09 U/patient per 4 wk ($P = 0.0001$) during each of the three 4-wk periods when compared with baseline. For placebo patients, the transfusion requirements increased significantly to an average of 0.44 U/patient per 4 wk ($P = 0.04$) during the third 4-wk period.

The fact that differences from baseline for placebo patients were significant during the third 4-wk period but not the first, despite similar means, can be explained by the use of a nonparametric test, which compares ranks not means. When the number of units administered per 4 wk was compared between groups (Kruskal-Wallis test) for each of the three 4-wk periods, the data showed that EPO patients were given significantly ($P \leq 0.005$) fewer transfusions (by at least 0.25 U/patient per 4 wk) than placebo patients. Figure 2 shows the mean number of units transfused per 4 wk during the 6 months prestudy and for the three 4-wk periods on-study, by group.

Amelioration of Anemia

As shown in Table 7, 61 (78%) of 78 patients treated with EPO ameliorated their anemia (reached a hematocrit of 35% or six hematocrit points above baseline) by Week 6, and 69 (88%) of 78 did so by Week 12 (Figure 3). In contrast, only 18 (24%) of 74 placebo patients ameliorated their anemia by Week 6, and 25 (34%) of 74 did so by Week 12. The results in the placebo patients can generally be attributed to transfusions and iron repletion. When the amelioration of anemia data was subjected to analysis by the Cochran-Mantel-Haenszel test of nonzero correlation for extent, there was a significant difference between groups at both Week 6 and Week 12 ($P < 0.0005$). In addition, the Cochran-Mantel-Haenszel ANOVA test showed a significant difference in the rate of anemia amelioration ($P < 0.0005$).

EPO Dosing

Dose levels were ranked by the weekly amount of EPO administered and then dichotomized into high-

TABLE 6. Change in red blood cell transfusions from baseline during the blinded phase

Group	N	Baseline Mean[a] (U/Patient per 4 wk)	Postmean (U/Patient per 4 wk)	Difference ± SE (U/Patient per 4 wk)	p[b]
EPO					
First 4-wk period	78	0.29	0.09	−0.21 ± 0.04	0.0001
Second 4-wk period	76	0.30	0.00	−0.03 ± 0.05	0.0001
Third 4-wk period	71	0.30	0.03	−0.27 ± 0.06	0.0001
Placebo					
First 4-wk period	74	0.25	0.42	+0.17 ± 0.11	0.65
Second 4-wk period	72	0.25	0.25	−0.00 ± 0.07	0.32
Third 4-wk period	69	0.25	0.44	+0.19 ± 0.08	0.04

[a] Baseline mean refers to the 6-month, prestudy transfusion rate.
[b] Wilcoxon signed-ranks test.

TABLE 7. Amelioration of anemia during the blinded phase

Week	Anemia ameliorated	EPO (N = 78)		Placebo (N = 74)		P	Odds Ratio	95%
		N	%	N	%			
6	Yes	61	78	18	24	<0.0005[a]	0.099[b]	(0.05, 0.20)[b]
6	No	17	22	56	76	<0.0005[c]	0.110[d]	(0.05, 0.24)[d]
12	Yes	69	88	25	34	<0.0005[a]	0.078[b]	(0.04, 0.16)[b]
12	No	9	12	49	66	<0.0005[c]	0.102[d]	(0.04, 0.23)[d]

[a] Cochran-Mantel-Haenszel test of nonzero correlation for extent.
[b] Mantel-Haenszel odds ratio.
[c] Cochran-Mantel-Haenszel ANOVA test for rate.
[d] Logit odds ratio.

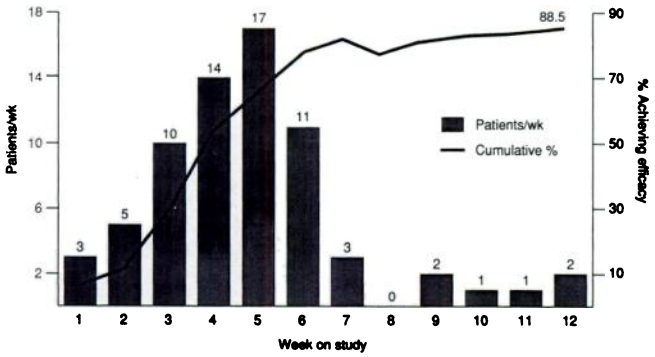

Figure 3. Amelioration of anemia in PD patients given EPO.

dose levels and low-dose levels (Table 8). High-dose levels (at least 5,000 U/wk) included 8,000 U thrice weekly, 4,000 U thrice weekly, 4,000 U twice weekly, and 5,000 U every week. Low-dose levels included 4,000 U every week and 4,000 U every other week. Patients who required the highest dose had the lowest mean baseline hematocrit, and patients who required the lowest dose had the highest mean baseline hematocrit ($P < 0.05$ using the Spearman rank correlation). Of the 145 patients who received EPO, 61 (42%) did not achieve a stable hematocrit during the study. Eleven (18%) of the 61 patients who never achieved stability had (at least during part of the study) been

TABLE 8. EPO dose producing stable hematocrit[a]

EPO Dose Level	N	%	Mean Baseline Hematocrit (%)	Mean Final Hematocrit[b] (%)
1. 8,000 U tiw	3	4	20.4	34.6
2. 4,000 U tiw	10	12	22.6	34.8
3. 4,000 U biw	23	27	23.7	34.8
4. 5,000 U qw	1	1	23.0[c]	36.0
5. 4,000 U qw	37	44	24.1	34.5
6. 4,000 U qow	10	12	25.2	32.3
Total	84	100	N/A	N/A

[a] A patient's hematocrit was considered stable if the hematocrit remained between 32 and 38% for at least 4 wk without a change in EPO dose or frequency of dosing and without the aid of red blood cell transfusions. tiw, thrice weekly; biw, twice weekly, qw, weekly; qow, every other week; N/A, not available. Some patients had more than one period of stability; the final period of stability was used for this analysis.
[b] The last hematocrit during the last period of stability.
[c] Note that the patient count = 1.

dosed once per week, which was inadequate for maintaining the hematocrit in the target range of 32 to 38%. For 4 (36%) of those 11 patients, a dosing schedule more frequent than once weekly was never attempted; therefore, the reason for their not achieving stability may have been inadequate dosing. All other patients who did not achieve stability received EPO more than once a week (at least during part of the

study). Other reasons for not achieving stability included periodic fluctuation outside the target range (below, $N = 38$; above, $N = 1$; both, $N = 8$) and EPO dose change (with the hematocrit remaining within the target range) that prevented the patient from meeting the rigorous criteria that were established for stability ($N = 3$). The use of phosphate binders and NSAID did not differ appreciably between patients who did or did not maintain a stable hematocrit.

Adverse Events

Blinded Phase. During the blinded phase, 74 EPO patients experienced 407 adverse events. Of those events, 58% ($N = 235$) were mild in severity and were considered unrelated or unlikely to be related to study medication. Thirty-seven percent ($N = 149$) were mild in severity but considered possibly, probably, or definitely related to study medication. Four percent ($N = 16$) were severe but were considered unrelated or unlikely to be related to study medication. One percent ($N = 5$) were severe and considered possibly, probably, or definitely related to study medication.

A similar distribution of adverse events was observed for the patients receiving placebo during the blinded phase. Of the 325 adverse events experienced by 63 placebo patients, 69% ($N = 223$) were mild and considered unrelated or unlikely to be related to study medication. Twenty-six percent ($N = 85$) were mild but considered possibly, probably, or definitely related to study medication. Four percent ($N = 13$) were severe and considered unrelated or unlikely to be related to study medication. Less than one percent ($N = 2$) were severe and considered possibly, probably, or definitely related to study medication.

Injection site complications were similar in frequency in EPO and placebo patients.

All Adverse Events After EPO Administration During the Study. All adverse events occurring while the patients were receiving EPO were evaluated together. Of the 145 patients who received EPO at any time during the study, 138 patients experienced 2,205 adverse events. Of those events, 74% ($N = 1,629$) were mild and were considered unrelated or unlikely to be related to study medication. Twenty-two percent ($N = 478$) were mild but considered possibly, probably, or definitely related to study medication. Three percent ($N = 75$) were severe but considered unrelated or unlikely to be related to study medication. Less than one percent were severe and considered possibly, probably, or definitely related to study medication.

Six patients had adverse events considered possibly or probably related to study medication and graded as severe or life threatening. During the blinded phase, four patients had seven such events; during the maintenance phase, three patients had four such events.

Deaths

Thirteen patients died on-study or after removal from the study. During the blinded phase, two patients receiving EPO and one patient receiving placebo died. During the maintenance phase, five patients initially randomized to EPO and five patients initially randomized to placebo died. Six deaths were judged by the investigator as unrelated to study medication, and six were judged as unlikely to be related.

TABLE 9. Blood pressure control during the blinded phase[a]

Status	EPO[b] ($N = 71$)		Placebo[c] ($N = 70$)		p^d
	N	%	N	%	
Improved	7	10	18	26	0.0001
Equivocal	3	4	5	7	
No Change	22	31	33	47	
Worsened	39	55	14	20	
Total	71	100	70	100	

[a] See footnote 3 in Text.
[b] $P < 0.0005$, within-group analysis (normal approximation to the binomial test and likelihood ratio test).
[c] $P = 0.48$, within-group analysis (normal approximation to the binomial test and likelihood ratio test).
[d] Cochran-Mantel-Haenszel ANOVA test, stratified by hypertension; between-group analysis.

Blood Pressure Control

Blinded Phase. Patients' blood pressure control was considered in the analysis only if at least three baseline blood pressures were obtained within 1 month of the on-study date, if there were follow-up blood pressure determinations obtained at the appropriate times during the study, and if there was information about concomitant therapy either prestudy or on-study. Of the 152 study patients, 11 were not evaluable for the blood pressure control analysis. The blood pressure control analysis was designed to compare each patient's diastolic blood pressure and prestudy antihypertensive regimen with the subsequent (on-treatment) diastolic pressure and antihypertensive regimen. Baseline systolic and diastolic blood pressure was compared between groups with a two-way ANOVA. The time chosen for the blood pressure control analysis was Week 12 (the end of the double-blind period). Thus, at Week 9 compared with baseline, improved, equivocal, unchanged, or decreased blood pressure control was determined for each patient.[3] Table 9 shows that, at Week 12, 39 (55%) of the 71 evaluable EPO patients had worsened blood pressure

[3] Baseline diastolic pressure ±9 mm Hg, with no change in antihypertensive medications, was considered an unchanged status of blood pressure control. Blood pressure control was considered equivocal if diastolic blood pressure decreased at least 10 mm Hg from baseline with the initiation or intensification of antihypertensive medications or if diastolic blood pressure increased at least 10 mm Hg with a less intense regimen of medication. Improved blood pressure control was defined as a diastolic blood pressure that decreased or remained at the baseline level, with a less intense antihypertensive regimen or as a diastolic blood pressure that decreased with no change in medication. Decreased blood pressure control was defined as no change or an increase in diastolic blood pressure with the initiation or intensification of antihypertensive medications or as an increase in diastolic pressure of at least 10 mm Hg with no change in medications.

control. Significantly ($P < 0.0005$) more EPO patients had worsened rather than improved blood pressure control. Of the 70 evaluable placebo patients, only 14 (20%) had worsened blood pressure control ($P = 0.48$). Blood pressure control was significantly worse in patients receiving EPO ($P = 0.0001$), indicating that EPO therapy or an increasing hematocrit may be associated with worsening of blood pressure control.

Of the 40 evaluable EPO patients who were hypertensive before enrollment, 25 (62%) had worsened blood pressure control ($P < 0.0003$). Of the 40 evaluable placebo patients who were hypertensive before enrollment, only 9 (22%) had worsened blood pressure control ($P = 0.39$). The between-group analysis of this hypertensive subset of patients also shows that EPO therapy was associated with decreased blood pressure control ($P = 0.0001$).

Of the 31 evaluable, nonhypertensive EPO patients, 14 (45%) had worsened blood pressure control ($P < 0.003$). Of the 30 evaluable, nonhypertensive placebo patients, only 5 (17%) had worsened blood pressure control ($P = 1.0$). The between-group analysis of this nonhypertensive subset of patients again showed that EPO therapy was associated with worsened blood pressure control ($P = 0.02$). In addition, hypertensive patients receiving EPO were more likely to experience worsening blood pressure control than were nonhypertensive patients receiving EPO (62 versus 45%).

Maintenance Phase. Blood pressure control status after 24 wk of EPO therapy (*i.e.*, at Week 24 for EPO patients and at Week 36 for placebo patients) was determined for all evaluable patients and compared with the status after 12 wk of EPO therapy. Patients had to have received at least 24 wk of EPO therapy to be evaluable for this analysis. Sufficient data to determine blood pressure control status at Weeks 12 and 24 for EPO patients and Weeks 24 and 36 for placebo patients were also required for evaluability. Thirty-seven (72.6%) of 51 patients whose status was worsened after 12 wk still had worsened status after 24 wk. In contrast, only 13 (22.8%) of 57 patients whose blood pressure control status was not worsened after 12 wk had worsened status after 24 wk. To test the hypothesis that one's status after 12 wk of EPO therapy is predictive of one's status after 24 wk, patients were categorized as to whether their status after 12 and 24 wk was the same or not. There was a highly significant ($P < 0.0005$) agreement between 12- and 24-wk status.

Blood Chemistries

The baseline renal, liver function, electrolytes, coagulation, and metabolic parameters were similar across the two treatment groups. There were no significant between-group changes at Week 12. In the EPO group, there was a marginally significant ($P = 0.05$) increase in creatinine from baseline, but this change is not of clinical significance. In addition, in the EPO group, there was an increase in phosphorus from 5.52 to 5.92 mg/dL ($P = 0.04$), a reduction in cholesterol from 229.06 to 215.69 mg/dL ($P = 0.02$), and an increase in PTT from 25.27 to 26.43 ($P = 0.0001$). In the placebo group, the cholesterol fell by Week 12 from 243.34 to 212.98 mg/dL ($P = 0.0001$).

DISCUSSION

Data from this randomized, double-blind, multicenter clinical trial show that EPO is both safe and effective when self-administered sc by ESRD patients undergoing peritoneal dialysis.

The results of the hematocrit, transfusion requirement, and amelioration of anemia analyses show that patients treated with EPO have substantial improvement when compared with patients treated with placebo. At Week 12, the mean hematocrit for the EPO group was 10.2 hematocrit points higher than the baseline hematocrit, whereas for the placebo group, the difference was 0.3 points. At Week 12, significant changes in red blood cells ($P = 0.0001$) and hemoglobin ($P = 0.0001$) were also seen between groups. EPO patients were given significantly ($P = 0.01$) fewer transfusions than placebo patients. Of the 34 EPO patients who required transfusions in the 6 months before the study, only 4 (12%) required transfusions during EPO treatment. Those transfusions were administered during the first 4-wk period of the study. Of the 31 placebo patients who required transfusions during the 6 months before the study, 15 (48%) required transfusions during the first 4-wk period, 10 (32%) required transfusions during the second 4-wk period, and 17 (55%) required transfusions during the third 4-wk period. By Week 12, 88% of EPO-treated patients had amelioration of their anemia compared with 34% of placebo-treated patients ($P < 0.0005$); 68% of the placebo-treated patients whose anemia was ameliorated did so because of transfusions.

Of the 145 patients who received EPO, 84 (58%) maintained a stable hematocrit of between 32 and 38% during the study. The dose most frequently needed to maintain a stable hematocrit was 4,000 U one time each week, which was received by 37 (44%) of the 84 patients who maintained a stable hematocrit. Patients who required the highest dose had the lowest mean baseline hematocrit, and patients who required the lowest dose had the highest mean baseline hematocrit.

During the first 12 wk, in a significant number of patients ($N = 39$, 55%), EPO therapy was associated with worsening of blood pressure control. Frequent monitoring of blood pressure was carried out, and antihypertensive therapy often had to be initiated or intensified. Patients with preexisting hypertension were at a slightly greater risk of experiencing increases in blood pressure control than were nonhypertensive patients. During the blinded phase, 62% of hypertensive patients receiving EPO experienced an exacerbation of hypertension, whereas only 45% of nonhypertensive patients developed hypertension

while on EPO. With careful monitoring, however, the occurrence of severe hypertensive events could be minimized, as demonstrated in this study. Even though 55% of EPO patients experience decreased blood pressure control compared with 20% of placebo patients, it is notable that only one hypertensive event graded severe or worse (as judged by the investigator) occurred in the EPO group. Thus, the prompt and effective treatment of hypertension, as carried out in this study, is possible and mandatory in PD patients receiving EPO.

After 24 wk of EPO therapy, 72.6% of patients whose blood pressure control deteriorated after 12 wk still had worsened hypertension after 24 wk. In contrast, only 22.8% of patients whose blood pressure control status was not adversely affected after 12 wk had deterioration of blood pressure control after 24 wk. A highly significant ($P < 0.0005$) concordance between 12- and 24-wk status was observed. Therefore, blood pressure control status at 12 wk is likely to persist to 24 wk.

In EPO patients, ferritin decreased significantly, which was expected because of increased hematopoiesis. No other clinically significant differences were found in the analyses of the laboratory data. EPO had no clinically significant effect on serum phosphorus levels or on patients' phosphate binder requirements.

No major self-administration problems were reported by patients. Compliance to keeping diaries, in which dosing and blood pressure information were recorded, was high. Those practices should transfer easily to the clinic.

These findings confirm and extend the results of uncontrolled studies in the literature, including data on iv, sc, and ip EPO use. Limited data are available on the effects of iv EPO in PD patients. When low doses of EPO were given by Hirasawa *et al.*, little response was seen (25). Appropriate dose increases (to 6,000 U/wk), however, resulted in an improvement in the response. Nasu *et al.* administered EPO iv to nine anemic PD patients once per week (20). After 18 wk, hematocrits rose from an average of 24 to 33% with an average maintenance dose of 13,300 U/wk.

The response of PD patients to sc EPO administration, as reported here, has been more widely studied. Lui *et al.* have documented that a weekly dose of 80 to 100 U/kg sc effectively raises the hemoglobin in PD patients, with no advantage with more frequent administration (21). This has been confirmed in a large, multicenter study, as well as in many smaller, single-center studies (26,27). Not all patients respond, however, as documented by MacDougall *et al.* (23). In that study, 4 of 15 PD patients responded poorly to sc EPO, two because of myelofibrosis. It appears that refractoriness to EPO in PD patients mirrors that seen in HD patients, except that acquired iron deficiency occurs less frequently in the PD group (28).

EPO administered ip has been shown to be effective in raising the hematocrit in adults and children on PD, particularly when administered into a dry abdomen or with a small amount of dialysate and a long dwell time (17–19,29). Additional issues have been raised about the use of ip EPO, including its adherence to dialysate bag or tubing, its biocompatibility in dialysate, and its route of absorption from the peritoneal cavity. Minimal amounts of EPO adhere to plastic *in vitro*, to dialysate bags, or to tubing (19,20,30). There is no need to seek an alternative vehicle for EPO to address this issue because it is not a clinical problem. Similarly, there is no interaction between dialysate and EPO that would render the EPO less potent (19,20). The precise mechanism of absorption of EPO from the peritoneal cavity, however, remains unresolved. In studies by Ateshkadi *et al.*, 64% of an ip dose was unaccounted for in plasma or effluent dialysate during a 96-h study (17). EPO is a glycoprotein with a molecular size of 30,400 d. As such, it should be absorbed via subdiaphragmatic lymphatics, as are other macromolecules (31–33). Whether it also accumulates in the diaphragm and abdominal wall has not been adequately studied.

The dosage requirements for EPO in this study were substantially lower than those used to maintain similar hematocrit levels in HD patients (34). Whether this reflects the route of administration or a unique benefit of PD (15) cannot be determined by this study.

The side effect profile of EPO in PD patients reported in the literature is similar to that seen in HD patients and reported here (23,26). Minor side effects include myalgias and burning at the site of sc injection (the latter attributable to the citrate vehicle) (35). A rise in blood pressure is seen in 25 to 30% of PD patients in most series, although some investigators suggest that this may be less commonly seen than in HD patients (26). Studies documenting an increase of seizures or adverse vascular events such as myocardial infarction, cerebrovascular accidents, or limb ischemia have not appeared in the literature.

Iron deficiency may occur in PD patients receiving EPO related to low iron intake or gastrointestinal blood loss due to the uremic bleeding tendency, combined with the iron demands of EPO-driven erythropoiesis. Because of the lower doses of EPO (and concomitant lower demand for iron) used in PD patients compared with those on HD and the absence of dialyzer/tubing blood loss, iron needs are more modest in PD patients using EPO and may be met in many cases by oral iron supplementation (23,28). Intravenous iron is still required in some patients, however.

Both solute transport and ultrafiltration have been studied in PD patients before and after the correction of anemia with EPO (23,36–48). Those studies are difficult to compare because of variations in methodology, although the majority have found no effect or a slight increase in creatinine dialysate to plasma ratio, mass transfer area coefficient, or peritoneal clearance. No adverse clinical effects of these findings have been

APPENDIX: PRINCIPAL INVESTIGATORS/SITES

Site	Principal Investigator	Site
University of California at Los Angeles	Allen Nissenson, MD	01
St. Joseph's Hospital, Orange, California	Dominick Gentile, MD	03[a]
Rush-Presbyterian-St. Luke's Medical Center	Stephen Korbet, MD	04
Indiana University Medical Center	Richard Hamburger, MD	05
Johns Hopkins University	Alan Watson, MD	06
Massachusetts General Hospital	Cecil Coggins, MD	07[a]
University of Michigan Medical Center	Richard Swartz, MD	08
Henry Ford Medical Center	Mark Faber, MD	09
University of Missouri	John Van Stone, MD	10
University of North Carolina	William Mattern, MD	11
Bowman Gray School of Medicine	John Burkart, MD	12
Cleveland Clinic Foundation	Martin Schreiber, MD	13
University of Wisconsin	Stephen Zimmerman, MD	14
Dialysis Institute of Indiana	Tim Taber, MD	15[a]
Dallas Nephrology Associates	Ronald Smith, MD	16[a]
University of Florida, Gainesville	Donald Mars, MD	18[a]

[a] Centers 03, 07, 15, 16 and 18 were combined and called Center 99 for analysis purposes, as these centers randomized fewer patients than any others.

reported. Peritoneal membrane function was not systematically evaluated in this study, but no changes in routine blood chemistries or dialysis prescription occurred, suggesting stable membrane function.

The availability of recombinant EPO has greatly improved the lives of patients with ESRD. Knowledge is still accumulating regarding the use and effects of EPO in patients on PD, and several critical questions remain to be answered (49).

(1) At what hematocrit level and when in the predialysis or dialysis course should EPO be started in PD patients? Recent studies by Golper show that the concomitant initiation of EPO and PD results in an increased hematocrit response compared with starting EPO after PD has been initiated for some time (50), suggesting that PD alone has a salutory effect on the anemia of ESRD. Data are needed as well relating patient functional capacity at various levels of hematocrit .

(2) What is the best route of administration of EPO in PD patients? It is apparent that iv, sc, and ip EPO can be effective in this population if used properly. The goal should be to tailor the route to the needs of the patient. Perhaps the daily sc route, for example, might be the best for minimizing hypertension because of the slow steady rise of hematocrit, whereas the ip route would be best tolerated by children (24,51).

(3) What should the target hematocrit level be? Although various organs may respond differently to anemia, whole patient data are not currently available that establish optimal hematocrit targets to maximize oxygen utilization. Near-normal levels of hematocrit have recently been reported to be safe and beneficial in dialysis patients (52–54).

(4) What are the effects of the correction of anemia on peritoneal membrane function? Although several studies have addressed this question (23,36–48), as outlined above, there is still considerable disagreement. A clear understanding of this issue might provide new insights into the physiology of PD.

(5) What are the effects of a higher hematocrit on functional status and quality of life in PD patients?

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