A Comparative Study of Efficacy and Safety of the Lyophilized Powder Alpha-Erythropoietin and the Liquid Form Alpha-Erythropoietin for Hemoglobin Maintenance in Patients with Hemodialysis Treatment

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Background: *Insufficient production of erythropoietin (EPO) is the primary cause of anemia in patients with chronic kidney disease (CKD). The EPO treatment is an established treatment for renal anemia. The study investigated the therapeutic outcome between lyophilized powder and liquid form of EPO alpha by intravenous (IV) administration in hemoglobin maintenance of anemic treatment for CKD patients receiving hemodialysis.*

Material and Method: *Forty patients were randomly assigned to either lyophilized powder of EPO alpha (treatment, n = 21) or liquid form of EPO alpha (control, n = 19) for 12 weeks by IV administration. The hemoglobin was maintained within the target range of 10.0 to 12.0 g/dL by adjusting the dosage of EPO. The clinical and biochemical profiles including transferrin saturation and ferritin were measured. Adverse events were documented.*

Results: *The mean hemoglobin of both groups at baseline was 11.2±0.6 g/dL. Mean hemoglobin and mean hematocrit levels at baseline, and follow-up data of both groups were not statistically different. The mean weekly dosage of EPO in the treatment and control groups had no statistical significance within the same group and between groups as well. Stable hemoglobin levels were maintained without EPO dosage adjustment in the majority of patients in both groups (treatment group, 90.5%, control group, 94.7%). During the 12-week study period, no serious side effect was detected.*

Conclusion: *The present study demonstrated that the lyophilized powder of EPO alpha was effective and safe as the standard liquid form of EPO alpha when it was administered by IV route in hemoglobin maintenance of anemia treatment.*

Keywords: *Anemia, Hemodialysis, Erythropoietin*

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The major pathogenic factor causing anemia in end-stage renal disease (ESRD) is the decreased synthesis of erythropoietin (EPO) in diseased kidneys[1]. EPO is effective for the improvement of quality of life and overall sense of wellbeing in dialysis patients[2,3]. Several clinical recommendations suggest using EPO to correct anemia in dialysis patients[4,5]. The data from the Thailand Renal Replacement Therapy Registry whose annual reports of chronic dialysis patients since 1997 indicate that patients with hematocrit of 33% or more had a better survival rate than those with less than 33%[6]. Therefore, EPO is recommended for using in hemodialysis patients who have a hemoglobin level of less than 10 g/dL[7], taking into consideration specific patient characteristics such as functional and cognitive status, life-expectancy, and other factors[8,9].

HEMAX® is lyophilized powder of EPO alpha, a 165-amino-acid glycoprotein produced by recombinant DNA technology in genetically modified mammal cells. Its molecular weight is 30.4 kDa and its amino acid structure is identical to that of the natural EPO. The maximum plasma concentration is achieved 15 minutes following the administration of an intravenous (IV) dose and between five and 24 hours following subcutaneous administration as a single dose. HEMAX® half-life is four to 13 hours post IV or subcutaneous administration. The recommend initial dose in adult anemia associated with chronic kidney disease (CKD) patients is 50 to 100 IU/kg by IV or subcutaneous routes, two or three times a week[9].

Since the costs of renal replacement therapy and medications are high, only few patients can afford the treatment, particularly patients in developing

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countries like Thailand. In addition, standard reference EPO product treatment is still expensive and not affordable in developing countries although it was used extensively. The purpose of the present study was to evaluate the safety and efficacy of the lyophilized powder of EPO alpha (HEMAX®) by IV administration to CKD patients receiving hemodialysis. Our goal was to determine if the lyophilized powder of EPO alpha would maintain hemoglobin and hematocrit levels as well as the standard liquid form via IV administration, but with a substantial reduction in the cost of recombinant human EPO.

Material and Method

The present research is a double blinded, randomized, controlled, single center, parallel-group study in the treatment of anemia of ESRD patients undergoing hemodialysis. Patients who had been on hemodialysis at the dialysis unit of the Nephrology Division, Phramongkutklao Hospital and College of Medicine, Bangkok, Thailand were eligible to enter the study. The patients' baseline dialysis prescriptions were maintained for the study period after enrollment. The study was approved by the Institutional Review Boards of the Phramongkutklao Hospital and College of Medicine. Eligible patients were randomized by a method of block randomization by a research nurses.

Inclusion criteria of the study were age, greater than 18 years old, undergoing regular hemodialysis at least three months with adequate dialysis by a single pool Kt/Vurea greater than 1.2 per dialysis treatment, adequate iron status (≥20% of transferrin saturation and ≥100 ng/mL of ferritin) and stable hemoglobin level of 10-12 g/dL with standard reference EPO alpha product (EPREX®) treatment at least three months.

Patient would be excluded by the following criteria: various identify causes of anemia such as gastrointestinal hemorrhage, hematologic malignancy, chronic infection, malnutritional anemia, active malignancy, pregnancy, severe hyperparathyroidism indicated by a serum parathyroid hormone level >9 x upper normal level, uncontrolled hypertension (mean systolic blood pressure >180 mmHg or diastolic blood pressure >110 mmHg), epilepsy or seizure within eight weeks before screening, active infection or hospitalization within three months before screening, had received blood transfusion within the last three months. Signed informed consent was obtained from all subjects after a thorough discussion of the protocol, its rational and potential risks.

Study protocol

All eligible patients were given standard liquid form of EPO alpha product and maintain the hemoglobin level at 10 to 12 g/dL for 12 weeks. Then, patients were randomly assigned to either the lyophilized powder of EPO alpha (treatment group) or the standard liquid form of EPO alpha product (control group) two or three times weekly by IV administration regimen for 12 weeks, 50 to 100 IU/kg/dose. The total weekly dosage was divided into two or three times following by hemodialysis session. EPO dosage was adjusted following hemoglobin change. If hemoglobin level increased more than 1.4 g/dL within two weeks, the dosage was reduced by 25 IU/kg/week. If hemoglobin did not increase more than 1 g/dL within the first four weeks, 50 IU/kg/week would be added to the total dose of 225 IU/kg/week. If hemoglobin level reached 10 g/dL, the dose would be adjusted to maintain hemoglobin level at 10 to 12 g/dL by researcher consideration. The lyophilized powder of EPO alpha (HEMAX®) was manufactured by the Pharmaceutical Laboratory Bio Sidus S.A. (Buenos Aires, Argentina). The study design was presented schematically in Fig. 1. The treatment dosage was the same as the previous one of standard liquid form of EPO alpha by IV administration.

Assessments of efficacy and safety

Eligible patients would be scheduled every four weeks to monitor hemoglobin level, reticulocyte count, iron status, dialysis dose (Kt/V), blood pressure, and clinical status. Mid-week collection of pre-dialysis blood samples were measured for lipid panel, liver function test, and hematology panel. Anti-EPO antibodies were performed at baseline and

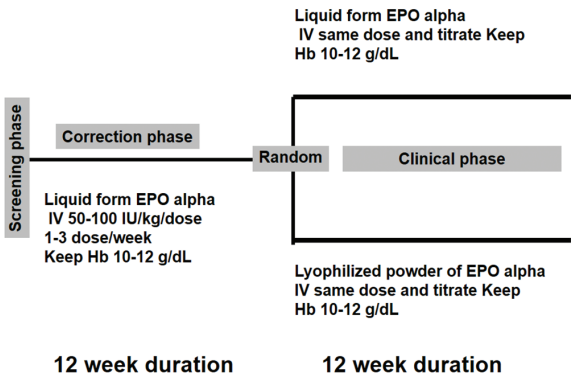

Fig. 1 Timeline in the randomized double-blinded, parallel-group study.

at the end of the maintenance phase. Serum patients were assayed for anti-EPO antibody detection by Radioimmunoprecipitationassay (RIPA), which is used to detect the presence of antibody to EPO quantitatively.

The primary efficacy outcome variable was the mean hemoglobin and hematocrit level at 12-week of treatment. Secondary efficacy outcome variables were the mean EPO alpha dose at 12-week of treatment and the proportion of patients who maintained a stable hemoglobin level (≥10.0 g/dL) without requiring an increase in total weekly EPO treatment.

Statistical analysis

Comparisons between treatment groups were carried out using the Independent t-test and repeated measures analysis of variance (ANOVA). Comparisons within groups were carried out using the Paired t-test and repeated measures ANOVA. Comparisons between treatment groups were carried out using the Chi-square test to assess whether there were any significant difference between groups in the number of patients who maintained stable hemoglobin levels without the EPO dosage adjustment and incidence of serious side effects. Measured values of the results were expressed in mean ± standard deviation. A significant level of 5% was considered statistically significant.

Results

Patients

Fifty-three patients in outpatient clinic were screened for possible study enrollment. Forty-four patients were eligible for the study criteria. Twenty-two patients were assigned to the treatment group, and 22 individuals to the control group, four patients were withdrawn from the study including three patients from treatment group by accidental infection and one patient from the control group by death unrelated to EPO. The rest of patients (n = 40) adhered to the EPO prescription protocol.

The mean age of the patients was 60±11.6 years (Table 1). The group consisted of 25 male and 15 female, all of whom were Asian. The comorbid diseases in the randomized population were listed in Table 1. No patient received blood transfusion during the study. There were no significant differences in gender, age, body weight, body mass index, duration of dialysis, hemoglobin, hematocrit, ferritin, transferrin saturation, and other laboratory profiles between two groups (Table 1).

Efficacy of treatment

Forty patients (21 in the treatment group and 19 in the control group) completed a 12-week study and were evaluated for efficacy. At baseline, the mean hemoglobin level was 11.28±0.61 g/dL in the treatment group compared to 11.21±0.61 g/dL in the control group. After initiation of treatment, mean hemoglobin and hematocrit levels during follow-up periods were similar in the two groups (Fig. 2). No statistically significant differences in the mean change in hemoglobin and hematocrit within group and between the two groups during study were found.

The mean weekly EPO alpha doses of the two groups were shown in Table 2. The mean weekly dose of EPO at weeks 0, 4, 8, and 12 was 138.7±95.3, 141.0±94.8, 141.0±94.8 and 138.1±96.3 IU/kg/week, respectively, in the treatment group, and 142.6±93.8, 138.7±75.7, 138.7±75.7 and 139.3±81.6 IU/kg/week, respectively, in the control group. The changes in the mean dosage of EPO alpha between the two groups from an initial of treatment (week 0) until 12-weeks of treatment (week 12) were not statistically significant. At the end point of the study, there was no significant differences in EPO dose between the treatment group and the control group (138.1±96.3 vs. 139.3±81.6 IU/kg/week, $p = 0.965$).

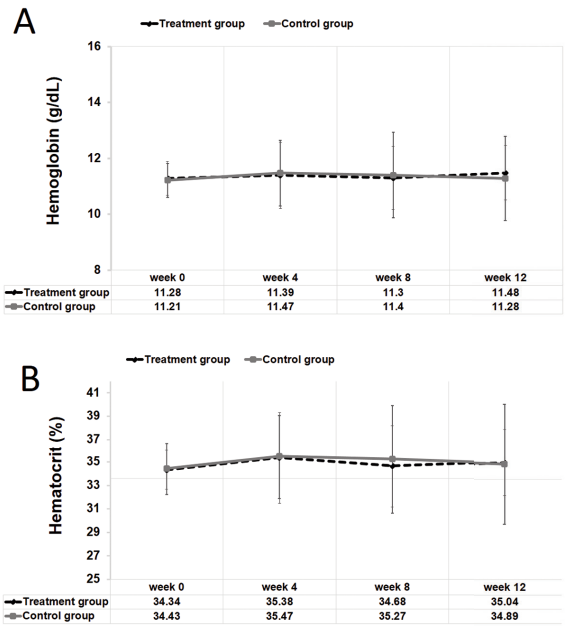

Fig. 2 Mean (± SD) hemoglobin (A) and hematocrit (B) in both groups remained stable throughout the study (p>0.05).

Table 1. Patient characteristics at baseline

	Treatment group (n = 21)	Control group (n = 19)	*p*-value
Male (n, %)	13 (61.9%)	12 (63.2%)	0.935
Age (years)	58.81±12.71	61.58±10.58	0.461
Duration of dialysis (months)	30.24±27.82	29.63±24.54	0.942
Comorbid disease			
Diabetes melllitus (n, %)	13 (61.9%)	13 (68.4%)	0.666
Hypertension (n, %)	19 (90.5%)	19 (100%)	0.488
Heart disease (n, %)	5 (23.8%)	5 (26.3%)	1.000
Hypertension (n, %)	1 (4.8%)	1 (5.3%)	1.000
Gout (n, %)	1 (4.8%)	2 (10.5%)	0.596
Dyslipidemia (n, %)	18 (85.7%)	16 (84.2%)	1.000
Body weight (kg)	59.03±10.45	58.02±10.59	0.764
Body mass index (kg/m^2)	22.58±3.25	22.31±4.16	0.816
Systolic blood pressure (mmHg)	135.33±17.05	134.63±24.03	0.915
Diastoilic blood pressure (mmHg)	70.71±14.31	67.05±12.77	0.401
Hemoglobin (g/dL)	11.28±0.61	11.21±0.61	0.697
Hematocrit (%)	34.34±1.68	34.43±2.21	0.887
Reticulocyte count (%)	1.70±0.66	1.65±0.56	0.769
Ferritin (ng/mL)	504.30±437.51	598.47±493.12	0.526
Transferrin saturation (%)	33.74±16.77	32.28±8.56	0.734
Intact-PTH (pg/mL)	164.12±136.57	236.40±191.39	0.174
BUN (mg/dL)	39.58±17.93	44.84±25.59	0.452
Serum creatinine (mg/dL)	6.83±2.49	8.45±3.40	0.091
Serum calcium (mg/dL)	9.27±0.93	9.16±1.76	0.806
Serum phosphorus (mg/dL)	3.90±1.09	3.97±1.75	0.864
Serum albumin (g/dL)	4.36±0.36	4.23±0.40	0.302

PTH = parathyroid hormone; BUN = blood urea nitrogen
Data are expressed as mean ± SD or as number (percentage) of patients. Comparisons between treatment groups using the independent t-test (continuous variables) and Chi-square test (categorical variables).

Table 2. EPO alpha dose at baseline and weeks 4, 8, 12

Assessment	EPO dose (IU/kg/week)		*p*-value (EPO dose between two groups)
	Treatment group (n = 21)	Control group (n = 19)	
Week 0	138.7±95.3	142.6±93.8	-
Week 4	141.0±94.8	138.7±75.7	-
Week 8	141.0±94.8	138.7±75.7	-
Week 12	138.1±96.3	139.3±81.6	-
p-value (within group)	0.830	0.355	0.852

EPO = erythropoietin
Data are mean ± SD; comparisons between treatment groups and within groups using the repeated measures analysis of variance (ANOVA).

There were no significant differences between the treatment and the control groups in the number of patients who maintained stable hemoglobin levels (≥10.0 g/dL) without EPO alpha dosage adjustment. In the majority of patients (treatment group, 90.5%, control group, 94.7%), stable hemoglobin

levels were maintained without the EPO dosage adjustment.

Change of blood pressure during study

Blood pressure changed during study is shown in Table 3. At baseline, there was no significant difference in blood pressure between the two groups. In addition, no significant difference was detected in systolic, or diastolic blood pressure between the treatment and the control groups throughout the study. Moreover, the lyophilized powder of EPO alpha was well tolerated, and additional antihypertensive treatment was not required in the both groups.

Change of biochemical profiles during study

The changes in mean transferrin saturation and ferritin values between the two groups for weeks 0 to 12 were not statistically significant. In addition, there was no significant change in blood urea nitrogen (BUN), serum creatinine, albumin, serum calcium, phosphate, and intact parathyroid hormone in the treatment group as compared to the control group at 12-week of treatment (Table 3). No significant difference between the two groups was detected in biochemical profiles.

Quality of life in hemodialysis patients

Quality of life during the study was measured. With regard to the SF-36 scores, both the physical component and the mental component did not significantly change from baseline in both groups. The differences in the changes in the SF-36 physical and mental scores between the two groups did not reach statistical significance.

Safety profiles

There were no clinically significant differences in the numbers and types of adverse events observed in the two groups. During the 12-week study period, the adverse events in both groups including dizziness and fatigue in three patients were reported. No any serious side effects were detected. In addition, serum antibodies against EPO at baseline and 12-week of treatment were not found in all patients.

Discussion

To our knowledge, the present study was the first randomized control trial of the safety and efficacy of the lyophilized powder of EPO alpha therapy in anemic CKD patient receiving hemodialysis by IV administration. The study demonstrated that the lyophilized powder of EPO alpha was therapeutic equivalence as standard liquid form of EPO alpha by IV administration in hemoglobin maintenance for anemic treatment in hemodialysis patients. There was no statistically significant difference in mean weekly dose of EPO alpha between the two groups. Hence, the results of the present study showed that switching from the standard liquid form of EPO alpha to the lyophilized powder of EPO alpha by IV administration was effective for maintaining tight, sustained, and predictable control of hemoglobin levels within target range in this patient population.

Only few clinical studies have reported on the lyophilized powder of EPO alpha regimen[10,11]. Two studies with the lyophilized powder of EPO alpha had also recently been reported. A prospective, open-label study evaluated the efficacy of treatment with the lyophilized powder of EPO alpha in 36 patients with cancer. In 73.5% patients, an increase in the level of hemoglobin was registered, and in 64.7%, its normalization was attained. Transfusional requirements were reduced by 50%[10]. One previous, randomized, placebo-controlled, multicenter trial was reported[11]. The lyophilized powder of EPO alpha administration, started after the first two weeks of life, reduced the transfusion requirement in premature infants with BW <800 g[11]. In the present study, the stable hemoglobin level was also maintained in more than 90%of hemodialysis patients without blood transfusion and a small portion of hemodialysis patients required the EPO dosage adjustment to maintain the hemoglobin level. This possibility may be related with a short treatment periods which affects patient's achieving hemoglobin maintenance.

Not only laboratory parameters, but also a general condition and quality of life of patients were shown that all factors were stable during 12 weeks treatment. The functional status, appetite, wellbeing, easily fatigued and dizziness were shown that no significant differences between two treatments. Adverse effects including rash, seizure, and uncontrolled hypertension were not found in all patients.

Recently, a significant increasing of the occurrence of erythropoietin-induced pure red cell aplasia (PRCA) which leaded to severe inhibition of red cell production and severe anemia, had been reported[12]. The extensive use of biosimilar erythropoiesis-stimulating agents led to an epidemic of PRCA in Thailand[13,14]. One of the factors which was a cause of epidermic PRCA that seems to be differences among different brands of EPO[15].

Table 3. Changes in metabolic profiles from baseline to week 12

	Treatment group (n = 21)	Control group (n = 19)	*p*-value between two groups
Systolic blood pressure (mmHg)			
Baseline	135.30±17.10	134.60±24.00	0.915
Week 12	142.52±21.60	144.40±33.60	0.831
p-value	0.542	0.738	
Diastolic blood pressure (mmHg)			
Baseline	70.70±14.03	67.10±12.80	0.401
Week 12	73.50±12.60	70.30±11.70	0.410
p-value	0.229	0.307	
Serum ferritin (ng/mL)			
Baseline	504.30±437.51	598.47±493.12	0.526
Week 12	494.79±445.37	568.33±458.03	0.610
p-value	0.867	0.573	
Transferrin saturation (%)			
Baseline	33.74±16.77	32.28±8.56	0.734
Week 12	32.43±15.50	33.81±16.81	0.789
p-value	0.652	0.683	
BUN (mg/dL)			
Baseline	39.58±17.93	44.84±25.59	0.452
Week 12	44.09±16.62	37.32±13.93	0.173
p-value	0.110	0.244	
Creatinine (mg/dL)			
Baseline	6.83±2.49	8.45±3.40	0.091
Week 12	7.12±2.12	8.11±2.98	0.241
p-value	0.360	0.546	
Reticulocyte (%)			
Baseline	1.70±0.66	1.65±0.56	0.769
Week 12	1.64±0.62	1.58±0.61	0.784
p-value	0.572	0.718	
Serum albumin (g/dL)			
Baseline	4.36±0.36	4.23±0.40	0.302
Week 12	4.30±0.37	4.14±0.58	0.278
p-value	0.440	0.430	
Serum calcium (mg/dL)			
Baseline	9.27±0.93	9.16±1.76	0.806
Week 12	9.60±0.55	9.45±1.03	0.572
p-value	0.075	0.476	
Serum phosphate (mg/dL)			
Baseline	3.90±1.09	3.97±1.75	0.864
Week 12	4.05±0.95	3.40±0.90	0.033
p-value	0.552	0.178	
Intact-PTH (pg/mL)			
Baseline	164.12±136.57	236.40±191.39	0.174
Week 12	180.40±184.06	282.17±243.80	0.142
p-value	0.557	0.105	

Data are mean ± SD; comparisons between treatment groups using the independent t-test and comparisons within groups using the paired t-test.

However, there was a limited data of lyophilized powder and liquid form of EPO alpha in developing of PRCA. In the present study, antibodies against EPO were studied in all patients, the titer of serum anti-EPO antibody level were lower than 1/100,000, so that PRCA were not found. However, there were major limitations of the study including a short study period (only 12 weeks) and a small sample size. In general, patients receiving EPO for longer time may be more likely to develop an immune response against it. The

median duration of EPO treatment before PRCA diagnosis is ranging from one month to five years.

The demographic and baseline characteristics of patients were consistent with the general dialysis population and demonstrated a high prevalence of comorbid diseases. Hence, the study population was representative of patients who were on dialysis and treated for renal anemia in clinical practice. Based on the results of the present study, the lyophilized powder of EPO alpha was effective for maintaining the hemoglobin and there was also significantly lower weekly drug costs observed in the lyophilized powder of EPO alpha group compared with the liquid form.

In conclusion, the IV administration of the lyophilized powder of EPO alpha was safe and effective for maintaining the hemoglobin and hematocrit level and suitable for stabilization of hemodialysis patients who volunteered for the present study. Serious adverse effects were not detected, however, there were only 40 patients included in the present study. Long-term outcomes should be further evaluated.

What is already known on this topic?

Erythropoietin (EPO) alpha is effective for the improvement of quality of life and overall sense of wellbeing in dialysis patients. HEMAX® is lyophilized powder of EPO alpha, a 165-amino-acid glycoprotein produced by recombinant DNA technology in genetically modified mammal cells. Only few clinical studies have reported on the lyophilized powder of EPO alpha regimen[10,11]. Two studies in patients with cancer and premature infant, lyophilized powder of EPO alpha reduced the transfusion requirement and improved anemic symptoms.

What this study adds?

The IV administration of the lyophilized powder of EPO alpha was a safe and effective therapy for maintaining the hemoglobin and hematocrit level and suitable for stabilization of hemodialysis patients who volunteered for this study. Serious adverse effects were not detected in the present study.

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Potential conflicts of interest

None.

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การศึกษาเปรียบเทียบประสิทธิภาพ และความปลอดภัยของ alpha-erythropoietin ชนิด lyophilized powder กับชนิด liquid ในการรักษาระดับฮีโมโกลบินในผู้ป่วยโรคไตเรื้อรังที่ฟอกเลือดด้วยเครื่องไตเทียม

บัญชา สถิระพจน์, อุปถัมภ์ ศุภสินธุ์, พรรณบุปผา ชูวิเชียร

ภูมิหลัง: *สาเหตุหลักของภาวะโลหิตจางในผู้ป่วยโรคไตเรื้อรังเกิดจากขาดฮอร์โมน erythropoietin (EPO) ดังนั้น EPO จึงช่วยรักษาภาวะโลหิตจางได้ การศึกษานี้เป็นการศึกษาผลความเท่าเทียมกันในการรักษาภาวะโลหิตจางระหว่าง alpha-erythropoietin ชนิด lyophilized powder กับชนิด liquid โดยการบริหารยาทางหลอดเลือดดำ เพื่อการรักษาระดับฮีโมโกลบินของผู้ป่วยโรคไตเรื้อรังที่ฟอกเลือดด้วยเครื่องไตเทียม*

วัสดุและวิธีการ: *ผู้ป่วย 40 ราย สุ่มได้รับ alpha-erythropoietin ชนิด lyophilized powder จำนวน 21 ราย กับชนิด liquid จำนวน 19 ราย โดยการบริหารยาทางหลอดเลือดดำเป็นระยะเวลา 12 สัปดาห์ โดยปรับขนาดยาควบคุมระดับฮีโมโกลบิน 10-12 มก./ดล. แล้วติดตามอาการทางคลินิก ผลตรวจเลือด รวมถึงระดับ transferrin saturation และ ferritin และผลข้างเคียงของยา*

ผลการศึกษา: *ค่าเฉลี่ยฮีโมโกลบินของผู้ป่วยทั้งสองกลุ่มก่อนเริ่มศึกษาเท่ากับ 11.2±0.6 มก./ดล. ค่าเฉลี่ยฮีโมโกลบิน และค่าเฉลี่ยฮีมาโตคริตทั้ง 2 กลุ่ม ไม่แตกต่างกันตั้งแต่ช่วงเริ่มและหลังสิ้นสุดการศึกษา เช่นเดียวกันค่าเฉลี่ยขนาดยา EPO ต่อสัปดาห์ ในผู้ป่วยทั้งสองกลุ่มไม่มีการเปลี่ยนแปลงหลังการรักษา และไม่มีความแตกต่างกันระหว่างกลุ่มอย่างมีนัยสำคัญทางสถิติ ผู้ป่วยส่วนใหญ่ร้อยละ 90.5 ที่ได้รับ alpha-erythropoietin ชนิด lyophilized powder และร้อยละ 94.7 ของ alpha-erythropoietin ชนิด liquid มีระดับฮีโมโกลบินคงที่ โดยไม่มีการปรับขนาดยา EPO ในช่วงที่ทำการศึกษา นอกจากนี้ไม่พบผลข้างเคียงร้ายแรงใด ๆ ระหว่างการักษา 12 สัปดาห์*

สรุป: *การศึกษานี้แสดงให้เห็นว่า ยา EPO-alpha ชนิด lyophilized powder มีประสิทธิภาพ และปลอดภัยเท่าเทียมกับ EPO-alpha ชนิด liquid ในการรักษาภาวะโลหิตจาง เมื่อบริหารยาทางหลอดเลือดดำ เพื่อรักษาระดับฮีโมโกลบินในผู้ป่วยโรคไตเรื้อรังที่ฟอกเลือดด้วยเครื่องไตเทียม*