THE CLINICAL EFFECTS OF RECOMBINANT HUMAN ERYTHROPOIETIN FOR THE TREATMENT OF ANEMIA IN END STAGE RENAL DISEASE PATIENTS ON DIALYSIS

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Abstract. It has been widely accepted that recombinant human erythropoietin can improve renal anemia which in turn eliminates several complications that occur from giving blood transfusions repeatedly in chronic dialysis patients. While there are few studies of erythropoietin administration via the subcutaneous route, such studies have reported different results from the intravenous route traditionally recommended in the literature. We set a cross-over technique to assess the results and adverse effects of erythropoietin administered by different routes in two groups of our chronic hemodialysis and continuous ambulatory peritoneal dialysis patients. The purposes of this study were: 1) to verify the effectiveness of erythropoietin; 2) to test whether the subcutaneous route yields the same results as the intravenous route and if there is no difference, we will choose the former for the benifit and compliance of our patients; and 3) to find out any adverse effects.

INTRODUCTION

Anemia in chronic hemodialysis (HD) and continuous ambulatory peritoneal dialysis (CAPD) patients is derived from decreased production of erythropoietin (EPO) which is the major hormone produced by peritubular interstitial cells in the medulla of the kidney (Erslev, 1990). EPO usually stimulates proerythroblast in the bone marrow and enhances differentiation and proliferation of erythrocytes, but cannot correct anemia due to other causes such as blood loss, hematologic disorder, parasitosis and iron deficiency. Prior to the current use of recombinant human EPO, several treatments have been used in an attempt to combat anemia such as blood transfusion, ferrous preparation vitamin B_{12}, androgen or even parathyroidectomy but there has been no satisfactory results. Moreover, giving frequent blood transfusions or testosterone can create unfavorable adverse effects (Varet *et al,* 1990). Therefore, we set the clinical study of EPO to assess and compare its efficacy and side effects between those who were given it subcutaneously and intraveneously. Should the subcutaneous (SC) route of administration yield similar results to those of the intravenous (IV) route, we would choose the former method because of its convenience and compliance for the benefit of our patients.

MATERIALS AND METHODS

Fourteen cases of end stage renal disease (ESRD) were recruited to the study. In eight HD cases, seven were female and one was male with the age ranged from 20-64 years. Every patient had HD performed twice a week, and four cases of ESRD in this cohort were chronic glomerulonephritis (CGN) and four cases were chronic tubulointerstitial nephritis (CTIN). In six CAPD cases, two were male and four were female with the age range between 37-59 years. One case was CGN, four were CTIN and one was hypertension (HT). The selected patients had to have had: 1) regular HD or CAPD for not less than 3 months; 2) hematocrit (Hct) $\leq$ 23 vol% or hemoglobin (Hb) $\leq$ 7.5 g/dl; 3) no other causes of anemia; 4) blood pressure (BP) $\leq$ 170/100 mmHg; and 5) no other previously severe complications.

The cross-over technique of EPO administration conducted in this study was as follows. We classified the subjects into three groups as shown in Table 1. Four HD patients in Group 1 were initiated by SC injection of Epoietin beta (Epogin) 3,000 IU immediately after finishing every session of HD twice a week for a period of 12 weeks. Then we stopped giving EPO and let them pause through a wash-out period for 6 weeks. Later we

Table 1

Administration of Epoietin beta (Epogin®) according to cross-over technique.

Group	Dosage	Route	First interval	Washout period	Route	Last interval
1. 4 HD cases	3000 IU twice a week	SC	12 weeks or Hct = 30 ± 3 vol% Hb = 10 ± 1 g/dl	6 weeks	IV	12 weeks or Hct = 30 ± 3 vol% Hb = 10 ± 1 g/dl
2. 4 HD cases	3000 IU twice a week	IV	12 weeks or Hct = 30 ± 3 vol% Hb = 10 ± 1 g/dl	6 weeks	SC	12 weeks or Hct = 30 ± 3 vol% Hb = 10 ± 1 g/dl
3. 6 CAPD cases	3000 IU twice a week	IV	12 weeks or Hct = 30 ± 3 vol% Hb = 10 ± 1 g/dl	6 weeks	SC	12 weeks or Hct = 30 ± 3 vol% Hb = 10 ± 1 g/dl

switched to IV injection with the same dose by the same process for another 12 weeks. The same procedure was done in four HD patients in Group 2, except IV injections were given initially and followed by SC injections. We could not classify CAPD patients who mostly lived in other provinces into two groups as in HD patients due to the inconvenience and inability to comply with our program. Therefore, we arranged all six CAPD patient into Group 3 and followed the same procedure as those in Group 2. The time frame for each patient in this study was 30 weeks. Every patient had taken a ferrous preparation to increase iron storage, which is an important factor for EPO use to stimulate erythropoiesis (Faulds and Sorkin, 1989). During the first 12 weeks, if a patient's Hct rose to 30 ± 3 vol% or Hb to 10 ± 1 g/dl, we stopped giving EPO because of the high risk of thrombosis. During the wash-out period, if a patient's Hct dropped to the level at the beginning of the study, we would replace the EPO by another route for the final 12 weeks. Also, we would cease giving EPO any time during the last 12 weeks, if a patient's Hct or Hb rose to 30 ± 3 vol% and 10 ± 1 g/dl respectively.

RESULTS

A positive response to the given EPO was identified by rising Hct ≥ 3.0 vol% or Hb ≥ 1.0 g/dl above the value at the beginning of the study. Every patient in Group 1 responded well to SC EPO as shown in Table 2. The means of Hct before and after the first 12 weeks were 16.5 vol% and 26.0 vol%, respectively, *ie* the mean difference of Hct increased by 9.5 vol% (Table 4). After 6 weeks of the wash-out period, the mean Hct became 19.8 vol% while with the IV route it rose to 23.0 vol% at the end of the final 12 weeks (Table 3), or the mean difference of Hct increased by 3.2 vol% (Table 5). In Group 2, the mean of Hct before and after the IV route for the first 12 weeks were 17.3 vol% and 26.0 vol% (Table 2) or the mean difference of Hct increased by 8.7 vol% (Table 4). After the wash-out period, the mean Hct fell to 19.5 vol% (Table 3) but gradually rose to 23.5 vol% at the end of the last interval when replaced with the SC route, *ie* the mean difference of Hct increased by 4.0 vol% (Table 5). In Group 3, all CAPD patients responded as well as those in Group 2 as indicated by the rising mean Hct at the end of the first interval to 28.7 vol% (Table 2) *ie* the mean difference of Hct increased by 8.9 vol% (Table 4). After the wash-out period, the mean of Hct decreased to 22.5 vol% (Table 3) and rose to 27.6 vol% at the end of the last interval, an increase of the mean difference of Hct by 5.4 vol% (Table 5). The major complication for most patients after EPO administration was HT as determined by three consecutive measurements of BP; the diastolic BP was ≥ 10 mmHg higher than his or her original BP at the beginning of the study. There were two cases in Group 3 who developed hypotension, necessitating cessation of antihypertensive therapy.

DISCUSSION

All trends of Hct, Hb and red cell mass were in

Table 2

Changes of Hct means (vol%) in 3 groups before wash-out period.

Week / Group	0	1	2	3	4	5	6	7	8	9	10	11	12
1	16.5	16.8	17.5	18.5	20.3	20.3	21.5	21.0	22.3	23.0	25.5	23.5	26.0
2	17.3	17.7	18.3	18.5	20.0	22.0	23.0	24.3	23.3	24.3	25.0	26.0	26.0
3	19.8	20.2	22.3	23.3	24.0	25.0	25.0	25.2	25.8	27.0	27.8	27.2	28.7

Table 3

Changes of Hct means (vol%) in 3 groups after wash-out period. .

Week / Group	0	1	2	3	4	5	6	7	8	9	10	11	12
1	19.8	19.0	19.5	20.0	20.0	21.0	21.3	21.6	21.5	21.8	21.3	22.5	23.0
2	19.5	19.3	20.3	21.5	22.0	22.0	22.8	22.5	22.5	22.5	23.3	23.3	23.5
3	22.5	23.2	22.5	23.3	24.2	23.7	24.8	24.7	25.2	25.7	26.2	26.7	27.6

Table 4

Changes of Hct mean differences (vol%) in 3 groups before wash-out period.

Week / Group	1	2	3	4	5	6	7	8	9	10	11	12
1	0.3	1	2	3	3.8	5	4.7	5.8	6.5	8	7	9.5
2	-0.3	1	1.3	2.8	4.8	5	7	5	7	7.8	8.8	8.7
3	1	2.5	3.8	4.6	4.5	5.2	5.3	6	6	8	7.3	8.9

Table 5

Changes of Hct mean differences (vol%) in 3 groups after wash-out period.

Week / Group	1	2	3	4	5	6	7	8	9	10	11	12
1	-0.8	-0.3	0.3	0.3	0.3	1.3	1.5	1.8	2	1.5	2.8	3.2
2	-0.3	0.3	0.8	2	2.5	2.5	3.3	3	3	3	3.8	4
3	6	6	6	6	6	6	6	6	6	6	6	5.4

the same direction, therefore we used Hct as the indicator of EPO responsiveness. Reports indicate that responses are variable in relation to dose (Akigawa *et al,* 1988; Eschbach *et al,* 1987), *ie* to achieve the same rise in Hct in several patients it may be necessary to give different doses of EPO. Some patients required 45 IU/kg/week by IV route in three doses, while others need up to 1,500 IU/kg/week and every patient had a rise in Hct each time the EPO dose was increased. It was found that 95% of cases yielded Hct levels of 32-38 vol% (Eschbach *et al,* 1989) if the average dose of 450 IU/kg/week in three doses was administered.

In our study we gave 85-100 IU-kg/week or 6,000 IU/kg/week in two doses at the end of every HD session according to the schedule of our chronic HD program for convenience and economy due to high cost of Epoietin beta. Except for this consideration we would like to have observed the clinical response to lower doses of EPO given to both HD and CAPD Thai patients. From Table 4, the mean difference of Hct of the three groups increased by 9.5 vol% (Group 1), 8.7 vol% (Group 2) and 8.9 vol% (Group 3), with no significant differences. Administering Epoetin beta 6,000 IU/kg/week either by the SC route or the IV route in all 14 chronic dialysis patients, we found that 12 cases (85%) responded by increasing Hct by 8-10 vol%. For example, a patient who originally had a Hct of 15 vol% with symptoms of anemia had a Hct of 25 vol% after treatment, becoming symptomless and not requiring blood transfusion as was previously necessary.

Thus it was adequate for Thai patients to maintain their Hct at this level and not necessary to set the target of Hct as high as the 32-38 vol% (Abraham, 1990) used in other countries. Some literature reports claim that administering EPO by the SC route can attain the same Hct level using only 30-40% of the IV dose (Bommer *et al,* 1989; Besarab *et al,* 1990). Even though IV EPO has 100% absorption, its half-life is only 4-9 hours (Egrie *et al,* 1988; Kindler *et al,* 1989), whereas while SC EPO has only 25% absorption (Besarab *et al,* 1990) its half-life can be more than 24 hours. It was concluded that the sustained administration of EPO by the SC route resulted in better stimulation of Hct than by the IV route. But in Fig 1 of our study the mean differences of Hct of Group 1 and 2 before the wash-out period were

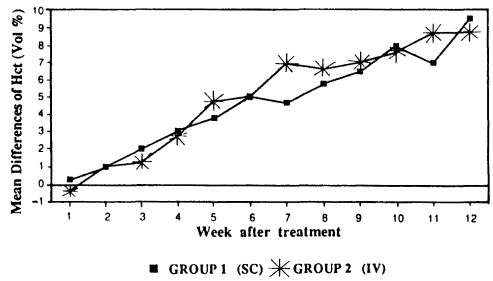

Fig 1—Linear graph depicted mean differences of Hct of Group 1 (SC) and Group 2 (IV) before wash-out period.

not remarkably different, possibly due to the limited time frame of our study, which was only 12 weeks; similar results have been reported (Graf *et al,* 1989). If a longer study had been possible we may have found that SC EPO was better than IV EPO. A point of note in this study was that the increase in mean differences of Hct of each group at the end of the first interval were higher than those at the end of the last interval (Fig 2, 3, 4) even when the same dose of EPO was given; the mean differences of Hct in week 12 before and after the wash-out period of Group 1 and Group 2 were not significantly different. In Group 3, though the trend looked similar to Groups 1 and 2 the differences were significant but we were unable to find a clear explanation. In our chronic renal failure patients who had an initially satisfactory response to EPO but temporarily ceased then restarted

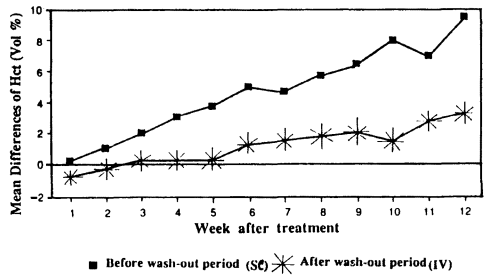

Fig 2—Linear graph depicted mean differences of Hct before wash-out period (SC) and after wash-out period (IV) in Group 1.

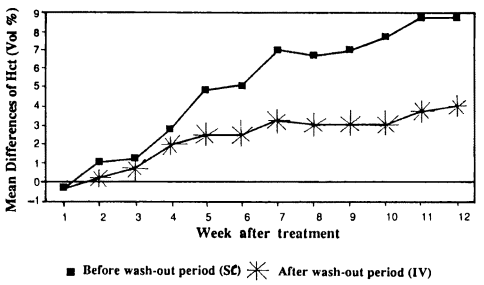

Fig 3—Linear graph depicted mean differences of Hct before wash-out period (SC) and after wash-out period (IV) in Group 2.

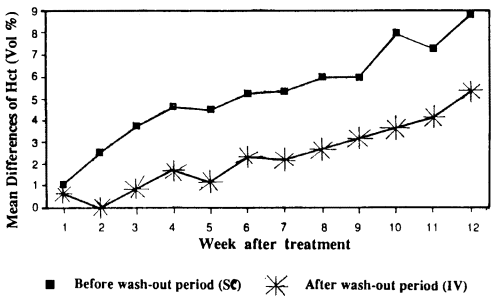

Fig 4—Linear graph depicted mean differences of Hct before wash-out period (SC) and after wash-out period (IV) in Group 3.

treatment the response was less than in the first treatment period. This observation merits further investigation.

Hyperkalemia, which according to the literature usually develops as a result of giving EPO (Abraham, 1990), did not occur significantly in our series. This might be due to the strict adherence of our patients to limited potassium intake. Twelve of 14 cases developed HT (Davidson *et al,* 1990; Spinowitz, 1990) but were controlled easily by increasing the dosage of antihypertensive drugs previously taken or adding a new drug. It is well known that prolonged severe anemia will diminish peripheral vascular resistance from hypoxia (Neff *et al,* 1971). When the renal anemia is abruptly corrected by giving EPO the peripheral vascular resistance will increase (Buckner *et al,* 1990) resulting in higher BP. There were two unusual HT cases in our study who had previously been controlled by antihypertensive drugs. They responded to EPO by a lowering of BP and we had to stop all antihypertensive drugs. This unorthodox phenomenon has been reported in the literature without any explanation of its mechanism. In severe anemia the kidney develops ischemia which in turn results in the activation of the renin-angiotensin system, potentially enhancing vasoconstriction, resulting in high BP. We propose the hypothesis that when renal anemia is corrected, the state of renal ischemia will disappear, resulting in diminishing release of renin-angiotensin, with resultant lowering of BP. Such a mechanism may be subject to individual variation in different patients and requires further investigation. In our study liver function tests were within normal limits and renal function tests remained as they were before therapy. No symptoms or signs of drug reaction developed in any patient.

Thus, we have studied the clinical effects of Epoietin beta for the treatment of renal anemia in ESRD patients who were put on HD and CAPD programs. Comparisons between the SC route and the IV route of administration in terms of increased Hct efficacy and other adverse effects according to the dosage and the time frame have been performed. We can conclude that: 1) both routes of administration yield very positive results of increasing Hct and there is no difference, especially in the first 12 weeks; 2) patients' responses to Epoietin beta given after the wash-out period in the last 12 weeks indicated satisfactory results, but the increasing Hct was remarkably lower than in the first interval; 3) HT developed in most patients but were easily controllable; 4) no remarkable hyperkalemia appeared as reported in the literature; 5) no drug reaction was discovered; 6) Epoietin beta 6,000 IU/week is adequate for Thai patients; and 7) the SC route of administration is highly recommended.

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