Comparison between Intravenous Recombinant Human Erythropoietin and Subcutaneous Injection in Thai Hemodialysis Patients

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Objective : *To compare the efficacy, safety and side effects between subcutaneous and intravenous route of erythropoietin administration in Thai hemodialysis patients.*
Design : *Retrospective study.*
Material and Method : *Retrospective study of hemodialysis patients who switched the route of erythropoietin administration from subcutaneous to intravenous in the Renal Unit Department of Medicine, Bangkok Metropolitan Medical College and Vajira Hospital and Thammasat University was carried out. All patients' information was obtained from the medical records.*
Results : *60 patients with stable hematocrit level in the last 3 months of the subcutaneous phase who were switched to intravenous route of erythropoietin administration for at least 6 months were recruited. The mean hematocrit level of patients in the last 3 months of the subcutaneous period was 30.49 $\pm$ 4.21 %. After switching to the intravenous route for 6 months, the mean hematocrit level was 30.24 $\pm$ 4.99%. Two patients had to increase the erythropoietin dosage and no side effects were found in the present study. The mean dosage of erythropoietin administered intravenously was not statistically different from the subcutaneous route. There was no correlation between age, sex, cause of renal failure, transferrin saturation, reticulocyte count, C reactive protein and the dosage of erythropoietin, together with the hematocrit level. No other side effects were encountered during the intravenous phase.*
Conclusions : *This study has shown that the subcutaneous erythropoietin in hemodialysis patients can be changed to the intravenous route in the same dosage with good response and stable hematocrit.*

Keywords : *Hemodialysis patient, Route administration, Erythropoietin, Hematocrit*

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It is widely accepted that human erythropoietin (rHUEPO) is essential for nearly all steps of red blood cell formation. The introduction of rHUEPO in clinical practice has improved the outcome and quality of life of ESRD patients, lessened the requirement of blood transfusion and an avoidance of transfusion related sequelae.

Initially the recombinant hormone was only given intravenously (IV). However, several years later the subcutaneous (SC) route of administration is increasingly used due to its longer half-life and provides similar efficacy to the IV route at a lower dose[1].

In 1997 the Dialysis Outcome Quality Initiative (DOQI) as well as the National Kidney Foundation (NKF) recommended the SC as the preferred route for erythropoietin administration and the European Best Practice Guidelines (EBPG) also stated a preference for SC administration in HD patients. This recommendation is based on data from numerous clinical studies which have demonstrated that SC administration is more efficacious than the IV route, reducing the dose requirement and thereby reducing costs[2,3].

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Although EPO-induced antibodies remained a very rare complication for many years, recently since 1998, the numbers of cases of EPO-related pure red cell aplasia (PRCA) due to the development of anti-EPO antibodies have increased dramatically[4]. Almost all cases were related to the SC route and the majority of cases have occurred in patients treated with erythropoietin alfa produced by Ortho-Biotech and market outside the United States (Eprex)[5,6]. Thus, at the end of 2002, health authorities decided to contraindicate the subcutaneous injection of epoietin alfa in Europe[7].

Besarab el al revised the meta-analysis of clinical studies comparing weekly IV and SC erythropoietin and indicated that the use of SC administration reduced the cost substantially[8]. Due to the discrepancy that still exits between IV and SC and no other reports regarding the consequences of switching from IV to SC in Thai hemodialysis patients ever studied before. The authors therefore conduct the clinical trial to compare the efficacy, safety and side effects between SC and IV route of EPO administration and study factors that may affect hematocrit response after switching from SC to IV route in Thai hemodialysis patients.

Material and Method

This study aimed to compare the efficacy, safety and side effects of SC and IV route of erythropoietin administration. The study was conducted according to good clinical practice and was approved by the Bangkok Metropolitan Administration Ethics Committee and written informed consent was obtained from all patients.

Design

This clinical trial was a retrospective study in patients who received HD treatment at the Renal Unit, Department of Medicine, Bangkok Metropolitan Medicine College and Vajira Hospital and Renal Unit Department of Medicine, Thammasat University.

Patients

The patients as defined criteria would be collected from information from the patients' medical record.

Inclusion criteria were as follows:

1. Patients 18 years or older on regular HD treatment

2. Treatment with SC erythropoietin alfa twice or three times weekly over the last 3 months with a stable hematocrit (28-36%) and switching to IV erythropoietin alfa at least for 6 months continuously.

3. Delivered KT/V of 1.2 or greater (HD thrice weekly) or 1.8 (HD twice weekly) (K, dialyzer-renal urea clearance, t=dialysis time, V=volume of distribution of urea) according to the Daugirdas formula (second generation)

4. Adequate iron status, defined as serum ferritin level of 100 ng/ml or greater and transferrin saturation greater than 20%. Iron supplementation was provided as required.

Exclusion criteria were the following:

1. Uncontrolled hypertension

2. Hemoglobinopathy, hemolysis or gastrointestinal bleeding

3. Infection or systemic inflammatory disease

4. Malignancy or epilepsy

5. Severe hyperparathyroidism indicated by serum parathyroid hormone level greater than 500 pg/ml

6. Serum aluminum level greater than 50 mg/ml, vitamin B12 level less than 200 pg/ml and folic acid level less than 2 ng/ml

7. Pregnancy or lactation

After obtained informed consent from the patients, laboratory information of all patients would be collected from personal medical records including CBC, BUN, creatinine electrolytes, liver function test, C reactive protein, KT/V, n PCR, absolute reticulocyte counts, iron status (serum iron, TIBC, ferritin, transferrin saturation), PTH, aluminum level, vitamin B2 level and folic acid level.

The other information which was obtained from each patients was age, gender, cause of ESRD and presence of ACEI.

Mean dosage of erythropoietin and hematocrit level 3 months before changing to IV route were recorded and were calculated from the total amount of EPO as the dose per kilogram of body weight for each patient. During 6 months of the IV phase, mean dosage of erythropoietin and hematocrit level were recorded. Other side effects such as pruritus, signs and symptoms indicated as pure red cell aplasia were also collected.

Statistical Analysis

The general information of patients at baseline would be analyzed descriptively by calculation of number and percentage of patients in each category. Hematocrit and dose level between SC and IV administration would be reported and analyzed by using the paired t-test statistical method. The hematocrit level and the dosage of erythropoietin alfa were analyzed correlation to various factors by using Chi-square statistical method.

Results

From 1 January 2003 to 31 December 2003, a total of 60 patients from 2 centers (Renal Unit, Department of Medicine, Bangkok Metropolitan Medicine College and Vajira Hospital and Renal Unit Department of Medicine, Thammasat University) were enrolled, of whom 14 were excluded due to iron deficiency. Of 46 patients remaining in the study group, there were 18 females and 28 males with a mean age of 59.36 years (range from 30-84 years). Mean serum ferritin, transferin saturation and hematocrit were 581±545.7, 36.7±14.1% and 30.49 ± 4.21 % respectively before changing from SC to the IV route. Almost all patients received erythropoietin alfa (Eprex) 4000 unit subcutaneously twice weekly. The other demographic data is shown in Table 1.

No correlations of various factors between sex, age, cause of ESRD, transferin saturation level, reticulocyte level, CRP and hematocrit level were found. The dosage of erythropoeitin also had no correlation with those factors.

After switching to the intravenous route, two patients had to increase the erythropoietin dosage, one case from 4000 IU once weekly into twice weekly since the third week after changing to the IV route as depicted in Fig. 1. Therefore, 96% of patients had good response to erythropoietin alfa with the IV route without increment of the EPO dosage. The mean dose of erythropoietin between SC injection was not significantly different from the IV route in 6 months after changing the method of injection as shown in Fig. 2.

The hematocrit levels in all 46 patients were plotted case by case in order to compare the level change between SC and IV administration as shown in Fig. 3. Almost all of the patients had a slight changed in the hematocrit level when they were switched from SC to IV. Similarly, the mean hematocrit level in phase of SC injection was not significantly different from the IV route at 6 months after changing the method of injection as shown in Fig. 4. Additionally, it indicated that the mean serum hematocrit was still in the target range of 28-36% both before and after switching from

Table 1 Basic information of patients who receive HD treatment at Renal unit, Department of Medicine, Bangkok Metropolitan Medicine College and Vajira Hospital and Renal Unit Department of Medicine, Thammasat University

Characteristic	Erythropoietin alfa (n=46)			
	N	%	Range	Mean ± SD
Gender				
Male	28	60.9	-	-
Female	18	39.1	-	-
Age (year)		-	30 - 84	59.36 ± 14.15
Cause of ESRD				
Diabetes	18	-	-	-
Hypertension	9	-	-	-
Chronic glomerular nephritis	7	-	-	-
CRP				
Negative	34	73.9	-	-
Positive	5	10.9	-	-
Dosage regimen (subcutaneous)				
4,000 IU once weekly	4	8.7	-	-
4,000 IU twice weekly	37	80.4	-	-
4,000 IU thrice weekly	1	2.2	-	-
Unknown	4	8.7	-	-
Chemistry laboratory				
Serum iron (ug/dl)	44	-	44 - 211	85.3 ± 39.2
TIBC (ug/dl)	44	-	150 - 331	225.8 ± 44.3
Transferrin saturation (%)	46	-	20.5 - 92.9	36.7 ± 14.1
Serum ferritin (ng/ml)	45	-	35 - 2,000	584.1 ± 545.7
Vitamin B12 (pg/ml)	45	-	314 - 2,202	1,093.9 ± 485.8
Folate (ng/ml)	45	-	222 - 15,149	3,648.5 ± 2,633.9
Reticulocyte (%)	34	-	0.5 - 10.5	1.7 ± 1.7
Creatinine (mg/dl)	35	-	3.4 - 13.9	8.9 ± 2.6
Hemoglobin (g/dl)	34	-	4.4 - 13.3	9.5 ± 1.7
Hemoglobin (%)	46	-	23.7 - 43.4	30.49 ± 4.21

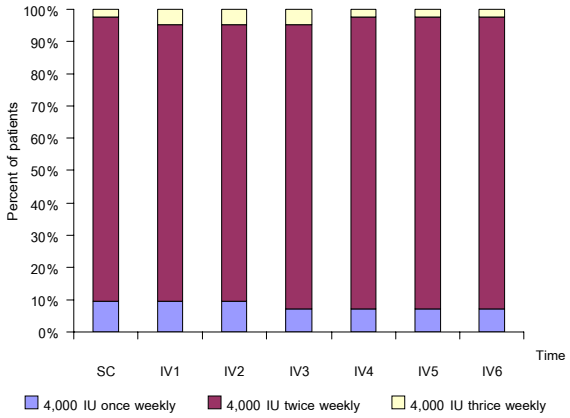


Fig. 1 Proportions of patients who received Erythropoietin alfa 4,000 IU once weekly, twice weekly and thrice weekly at SC and IV administration

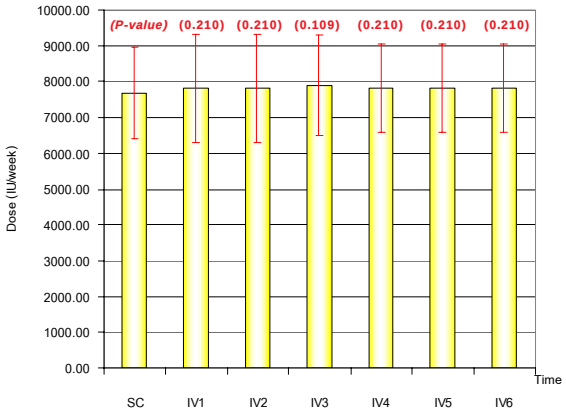


Fig. 2 Mean dose level of patients among SC and IV administration (No statistically significant difference, *P>0.05*)

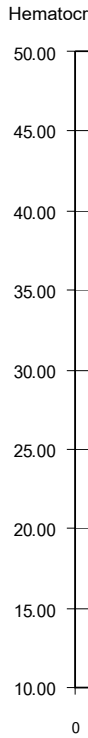


Fig. 3 Comparison of means hematocrit level between SC administration and IV administration through 6 month by each of 46 patients receiving erythropoietin alfa

SC to IV. Nevertheless, the distribution of hematocrit value at 6 months interval indicated a slight reduction of the hematocrit especially in the first four months.

Their mean hematocrit decreased nearly two points from 30.49 ± 4.21% toward 30.42 ± 4.58%, 30.21 ± 4.91%, 29.67 ± 4.91%, 29.22 ± 5.01%, 29.90 ± 5.13% and finally 30.24 ± 4.99% at the sixth month respectively, only the value at the 4th month was statistically significant from baseline. However, after 4 months, the mean hematocrit was increased towards target level. By 6 months after the IV route, the difference in magnitude of hematocrit change was less than 10% from baseline level as depicted in Fig 5. Treatment with the IV route was generally well tolerated. No side effects

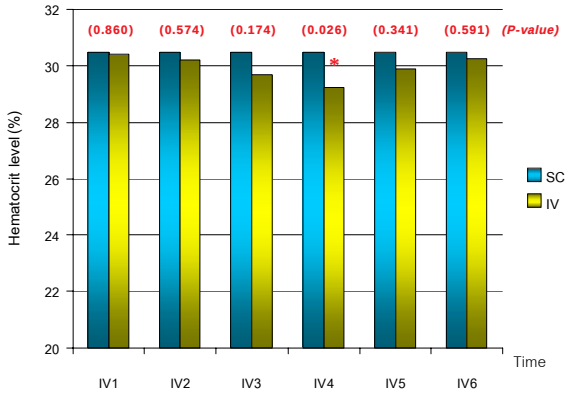
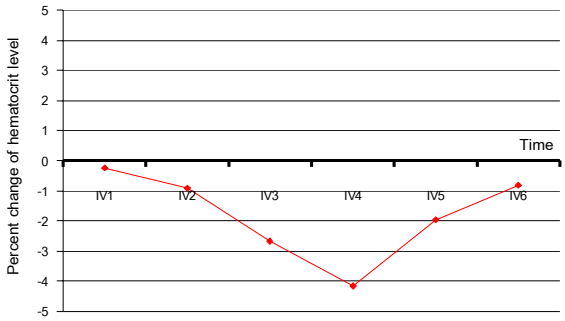


Fig. 4 Comparison of mean hematocrit level between SC administration and IV administration through 6 month in patients who received erythropoietin alfa (* Statistically significant difference at *P<0.05)*



level from SC
rough 6 month
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topoietin alfa in HD patients could be changed to IV in the same dosage with good response and stable hematocrit. A number of previous studies have compared the IV and SC route of administration of erythropoietin alfa[9-11]. In most of the reports, including the recent meta-analysis one also concluded that equivalent target hemoglobin levels are maintained with significantly lower dose of erythropoietin when administering SC compared with the IV route *(P<0.01)*[12]. Recently, however a significant increase in the occurrence of erythropoietin-induced pure red call aplasia (PRCA) which leads to severe inhibition of red cell production, has been reported. One of the factors that is clearly associated with the development of anti- EPO antibodies is its SC application[13-14]. In addition, there seems to be differences among different brands of erythropoietin[15]. The majority of cases reported were associated with the use of erythropoietin alfa distributed outside the US, which coincides with the removal of human serum albumin (HAS) from the ex-US formulation. In contrast, HAS was not removed from erythropoietin alfa form formulation in the US, where there has been no increase in the incidence of erythropoietin- induced PRCA. This together with the well known fact that in general SC administration of exogenous proteins are more immunogenic than IV administration led to the recommendation in July 2002 that IV application should be used for erythropoietin alfa. The only remaining barrier to IV administration is a potential increase in cost due to the possible need for higher doses of erythropoietin alfa. In Thailand, there are a reported cases of PRCA associated with anti-Recombinant-Human Erythropoietin[16]. Those patients recovered completely after renal transplantation together with disappearance of their anti-rHuEPO antibodies from their sera. This suggests that a natural molecule erythropoietin can terminate the humoral antibody response to its recombinant form.

In the present study, the authors found that the erythropoietin doses that were required to maintain the hematocrit level were not significantly different when switching from SC to IV. The hematocrit tended to drop at month 4, but increased towards target range (-4.17% from baseline, which is less than 10%) by 6 months. The cause of this reduction may be due to a different pharmacokinetic profile of erythropoietin which has longer half life when administered SC and the process of neocytolysis in which newly released RBC are destroyed when circulating erythropoietin levels decreased rapidly. This situation happens after IV erythropoietin because interdialytic accumulation does not occur. However, the magnitude of decrement is not large and when the authors adjusted the dose of erythropoietin, the hematocrit rose dramatically. The estimated drug cost was not different. According to the European Survey on Anemia Management (ESAM), there was also only a small non significant difference (9 IV/kg/wk) between SC and IV maintenance doses in hemodialysis patients. The IV route is convenient, does not produce any pain to the patient and is well tolerated. The authors observed no cases of pure red cell aplasia, accelerated hypertension or AVF thrombosis during the observation period. The erythropoietin doses were not significantly changed. The authors concluded that, on balance, the reduced risk of immunogenicity associated with IV administration in combination with other

potential benefits, such as elimination of injection pain and improved storage and handing should outweigh any potential increase in cost. Since the erythropoietin alfa is the main erythropoietin used widely in Thailand and was registered in the National Drug List. This study in Thai hemodialysis patients confirmed that switching from SC to IV as recommended in European countries is also a safe and efficient means of treating anemia in patients with end stage renal failure on regular hemodialysis.

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การศึกษาเปรียบเทียบผลของยาอีโพอิติน อัลฟ่า ที่ฉีดทางหลอดเลือดดำกับทางใต้ผิวหนังในผู้ป่วยไตวายเรื้อรังที่รักษาด้วยการฟอกเลือด

ธนันดา ตระการวนิช, ศุภชัย ฐิติอาชากุล

จากการศึกษากลุ่มผู้ป่วยไตวายเรื้อรัง 60 รายที่ได้รับการรักษาด้วยการฟอกเลือดที่หน่วยไตเทียม ภาควิชาอายุรศาสตร์ วิทยาลัยแพทยศาสตร์กรุงเทพมหานครและวชิรพยาบาล และคณะแพทยศาสตร์ มหาวิทยาลัยธรรมศาสตร์ โดยเปรียบเทียบผลเลือดก่อนและหลังการเปลี่ยนวิธีฉีดยาจากใต้ผิวหนังมาเป็นเข้าทางหลอดเลือด ผลการศึกษาพบว่าผู้ป่วยร้อยละ 96 ตอบสนองต่อยาอีโพอิติน อัลฟ่า ได้เป็นอย่างดีหลังเปลี่ยนวิธีการบริหารยา ระดับฮีมาโตคริตเฉลี่ยของผู้ป่วยหลังเปลี่ยนวิธีการบริหารยาเป็นการฉีดเข้าหลอดเลือดดำยังคงอยู่ในช่วง 28-36% และไม่แตกต่างจากก่อนการเปลี่ยนวิธีฉีดยา (ระดับฮีมาโตคริตขณะได้รับยาด้วยวิธีการฉีดเข้าใต้ผิวหนังคือ 30.49 $\pm$ 4.21 เปอร์เซ็นต์ และระดับฮีมาโตคริตที่เดือนที่ 6 หลังเริ่มได้รับยาด้วยวิธีการฉีดเข้าหลอดเลือดดำคือ 30.24 $\pm$ 4.99 เปอร์เซ็นต์ $p > 0.05$) โดยมีผู้ป่วย 2 รายจากทั้งหมด 46 รายที่ต้องเพิ่มขนาดของยาอีโพอิติน อัลฟ่าหลังจากได้รับยาด้วยวิธีการฉีดเข้าหลอดเลือดดำ และเมื่อเปรียบเทียบระดับฮีมาโตคริตเฉลี่ยของผู้ป่วยก่อน และหลังการเปลี่ยนวิธีการบริหารยา ไม่พบภาวะ pure red cell anemia ใน ผู้ป่วยที่ได้รับยาอีโพอิติน อัลฟ่า ด้วยวิธีฉีดเข้าหลอดเลือดดำ และผู้ป่วยส่วนใหญ่สามารถทนต่อยาอีโพอิติน อัลฟ่า ได้ดี

ผลการศึกษาสรุปได้ว่าผู้ป่วยไตวายเรื้อรังสามารถตอบสนองต่อยาอีโพอิติน อัลฟ่า ได้ดีหลังมีการเปลี่ยนวิธีการบริหารยาจากวิธีการฉีดเข้าใต้ผิวหนังเป็นการฉีดเข้าหลอดเลือดดำ โดยระดับฮีมาโตคริตของผู้ป่วยจะมีการเปลี่ยนแปลงไปจากเดิมไม่เกินร้อยละ 10 และไม่มีผลต่อประสิทธิภาพในการออกฤทธิ์ของยา อีโพอิติน อัลฟ่า ทั้งทางระดับฮีมาโตคริต และขนาดของยาอีโพอิติน อัลฟ่า ที่ผู้ป่วยได้รับ