Erythropoietin Dosage Adjustment Protocol in the Treatment of Anemia in Patients with Non-Dialysis-Dependent Chronic Kidney Disease Stage 4 and 5

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บทคัดย่อ : การศึกษาผลของยา Erythropoietin ทางคลินิกโดยใช้แนวทางการปรับยาในผู้ป่วยไตวายเรื้อรังระยะที่ 4 และ 5 ที่ยังไม่ได้รับการบำบัดทดแทนไตที่มีภาวะซีด

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ภูมิหลัง : ภาวะซีดในผู้ป่วยไตวายเรื้อรังเป็นภาวะที่พบได้บ่อย และปัจจุบันเป็นที่ยอมรับกันทั่วไปในการใช้ยาฮอร์โมนอีรีย์โธรปอยอีตีนในการรักษา **วัตถุประสงค์** : ผู้ศึกษาต้องการศึกษาผลของแนวทางการปรับยาฮอร์โมนอีรีย์โธรปอยอีตีนในผู้ป่วยไตวายเรื้อรังระยะที่ 4 และ 5 ที่ยังไม่ได้รับการบำบัดทดแทนไตที่มีภาวะซีด **วิธีการ** : เป็นการศึกษาแบบเปิดและไปข้างหน้าเป็นระยะเวลา 19 เดือน ของผู้ป่วยทั้งหมด 12 ราย ที่มีภาวะไตวายเรื้อรังระยะที่ 4 และ 5 ที่ยังไม่ได้รับการบำบัดทดแทนไตที่มีภาวะซีด (ฮีมาโตคริตน้อยกว่า 30%) ติดต่อกันอย่างน้อย 3 เดือน ค่าเฟอไรตีนในเลือดและค่าความอิ่มตัวของทรานซ์เฟอรีนมากกว่า 100 นาโนกรัมต่อเดซิลิตร และมากกว่าร้อยละ 20 ตามลำดับ โดยได้รับยาฉีดใต้ผิวหนังเริ่มต้นที่ขนาด 4,000 ยูนิตต่อสัปดาห์ และปรับขนาดยาตามแนวทางการปรับยาเพื่อรักษาระดับฮีโมโกลบินในช่วง 10-12 กรัมต่อเดซิลิตร **ผล** : มีผู้ป่วย 9 รายที่เข้าร่วมจนจบการศึกษา โดยมีค่าฮีโมโกลบินและฮีมาโตคริตในเลือดเริ่มต้นอยู่ที่ 8.76 ± 0.83 กรัมต่อเดซิลิตร และร้อยละ 26.33 ± 2.00 ตามลำดับ ผลการศึกษาพบว่าผู้ป่วยทุกรายมีค่าฮีโมโกลบินอยู่ในระดับที่ต้องการ ค่าเฉลี่ยของระยะเวลาในการรักษาระดับฮีโมโกลบินที่ 10-12 กรัมต่อเดซิลิตรติดต่อกันอย่างน้อยสามครั้งในการติดตามนัดอยู่ที่ 112.33 ± 45.11 วัน และขนาดยาเฉลี่ยอยู่ที่ 15555.56± 3711.84 ยูนิตต่อเดือน อย่างไรก็ตามพบว่าขนาดยาเฉลี่ยในผู้ป่วยไตวายเรื้อรังระยะที่ 4 อยู่ที่ 14400 ± 3577.71 ยูนิตต่อเดือน ซึ่งน้อยกว่าระยะที่ 5 อยู่ที่ 17000 ± 3829.71 ยูนิตต่อเดือน ผู้ป่วยทุกรายมีคุณภาพชีวิตดีขึ้นจากการตรวจโดยแบบสอบถาม และไม่พบผลข้างเคียงอื่นๆ ในการศึกษา **สรุป** : การใช้แนวทางการปรับยาฮอร์โมนอีรีย์โธรปอยอีตีนในผู้ป่วยไตวายเรื้อรังระยะที่ 4 และ 5 ที่ยังไม่ได้รับการบำบัดทดแทนไตที่มีภาวะซีดจากการศึกษานี้ สามารถเพิ่มความเข้มข้นของเลือดให้อยู่ในระดับที่ต้องการได้

คำสำคัญ : อีรีย์โธรปอยอีตีน ภาวะซีด โรคไตวายเรื้อรัง

Abstract

Background : Anemia is one of the most common complications among patients with chronic kidney disease (CKD). Erythropoietin (EPO) has been recommended for treatment of anemia in these patients. **Objectives** : To evaluate the clinical efficacy, safety and usefulness of EPO dosage adjustment protocol in the treatment of anemia in patients with non-dialysis-dependent CKD stage 4 and 5. **Method** : A nineteen months, open, non-comparative, prospective study of EPO administration was conducted in 12 patients. Eligible criteria included hematocrit (Hct) of less than 30% at least 3 consecutive months with serum ferritin level, and transferrin saturation level of higher than 100 ng/dl and 20%, respectively. Initial dose of EPO was 4,000 units/week subcutaneously and dosage was adjusted as in protocol to maintain the hemoglobin (Hb) level at 10-12 g/dl. **Results** : Nine patients were finally included into this

study. Baseline Hb and Hct were 8.76 ± 0.83 g/dl and 26.33 ± 2.00 % respectively. All patients reached to the targeted Hb, and mean duration to maintain target on 3 consecutive visits was 112.33 ± 45.11 days. The mean EPO doses was 15,555.56 ± 3,711.84 units/month. The mean doses of EPO in patients with CKD stage 4 (14,400 ± 3,577.71 units/month) was lower than those with CKD stage 5 (17,000 ± 3,829.71 units/month). General conditions including KDQOL-SF™ Version 1.3 score were improved. There were no significant adverse events. **Conclusion :** This study developed erythropoietin dosage adjustment protocol in the treatment of anemia in patients with non-dialysis-dependent CKD stage 4 and 5.

Keywords : Erythropoietin, Anemia, Chronic kidney disease

Introduction

Renal anemia is one of the major complications among chronic kidney disease (CKD). Multiple factors such as the deficiencies of iron and other nutrients, gastrointestinal bleeding were associated with this complication and inadequate erythropoietin is also one of the critical factors. Erythropoietin (EPO) is a siaglycoprotein hormone secreted primarily by a mature kidney in response to tissue hypoxia or the decrease in red blood cell mass. It stimulates erythrocyte production from the bone marrow[1]. The introduction of recombinant human erythropoietin (rHuEPO) therapy in 1987 offered a new way to manage the anemia problem, which affected more than 90% of these patients[2-3]. Several studies have reported the clinical efficacy of rHuEPO on several clinical aspects including anemia. In hemodialysis patients, effective EPO level could reach when administered subcutaneously or intravenously[4]. Less transfusion frequency and improvement in quality of life were also reported[3]. So, several clinical recommendations have suggested the using of EPO to correct anemia in these patients[5]. However, EPO treatment is expensive and not generalized affordable in many developing countries. The approved starting dose of epoetin alfa for correction of anemia of CKD in adults is 20-50 IU/kg body weight three times a week[6]. For maintenance of hemoglobin (Hb) levels, the dosage of epoetin alfa is adjusted by increments or decrements of 25%[7] to maintain the Hb within the target range of 11 to 12 g/dl[5] or between 10 to 12 g/dl[8]. When administered subcutaneously, the serum half-life of epoetin alfa ranges from 28 to 43 hours[9]. However the pharmacodynamics effect, as measured by an increase in red blood cell count, is evident for weeks to months. This reflects the life span (up to 120 days) of the red blood cells produced in response to EPO administration. In support of this concept, several studies in patients with CKD have reported that epoetin alfa administered (subcutaneously) up to every 4 weeks can achieve and maintain Hb levels within a specified target range[10-16]. These data suggest that dosing of epoetin alfa at extended intervals may be a potential treatment option. Changing the intervals between doses would be expected to provide significant benefits to patients by decreasing the frequency of injections, reducing the time spent in clinics, and potentially improving compliance. Furthermore, adjustment the intervals between doses of epoetin alfa would be the best choice for small hospital where did not have many drug items. This study was conducted to evaluate the EPO dosage adjustment protocol that adjusted by increments or decrements the frequency of injection of 25% of total monthly doses in the treatment of anemia in patients with non-dialysis-dependent CKD stage 4 and 5.

Materials and Methods

This is an open, non-comparative, prospective, cohort study at CKD outpatient clinic, Danchang hospital, between August 2014 and February 2016, among patients with non-dialysis-dependent CKD stage 4 and 5. Inclusion criteria included patients of age more than 18 years with hematocrit level less than 30% for at least 3 consecutive months, Serum ferritin level and transferrin saturation level for eligible patients were more than 100 ng/dl and 20%, respectively.

Exclusion criteria included patients who developed active infection or inflammatory disease, history of blood loss, especially gastrointestinal and vaginal bleeding, currently received immunosuppressive drugs, poor control blood pressure (Diastolic blood pressure more than 110 mmHg and systolic blood pressure more than 180 mmHg), history of allergy to erythropoietin or albumin, and history of convulsion.

Methods

1) Epoetin alfa dose and administration method

The Espogen™ (Epoietin alfa, LG Life Science Ltd.) was used in this study. As initial dose for all patients, 4,000 units/week was administered by subcutaneous route.

Dosage of EPO was adjusted according to hemoglobin change during visits. If hemoglobin (Hb) level was increased more than 2 g/dl within 4 weeks, the EPO dose would be reduced in frequency as in the protocol (table 1). If Hb level did not increase more than 1 g/dl within 4-6 weeks and was less than 10 g/dl, the dose was adjusted as in the protocol (table 1). If Hb reached 10 g/dl, the dose was adjusted to maintain Hb target between 10 and 12 g/dl according to researcher's adjustment.

Table 1 EPO dosage adjustment protocol

Step	EPO dose	Frequency
3	4,000	4 days
2	4,000	5 days
1	4,000	6 days
0	4,000	7 days
-1	4,000	10 days
-2	4,000	15 days

2) Iron therapy and blood pressure control

All patients were supplemented with ferrous fumarate (at least 200 mg/day) in with no diet restriction and blood pressure were controlled according to researcher's adjustment.

3) Methodology verification

The patients who signed the informed consent for this study have been initial blood collected for complete blood count (CBC), reticulocyte count, ferritin level, transferrin saturation, parathyroid hormone level. Stool occult blood was also be performed and patients was also evaluated by KDQOL-SF™ Version 1.3 score. During the follow up period, clinical evaluations included general symptoms and adverse effects were evaluated.

Blood pressure was recorded to evaluate the mean arterial blood pressure. Complete blood count was performed every 4-6 weeks for EPO dosage adjustment. At the end of this study, all eligible patients were also evaluated for general condition, KDQOL-SF™ Version 1.3 score and any adverse effects.

4) Efficacy and safety evaluation Methods

Categorical data was presented as mean and standard deviation due to normal distribution. To evaluate the clinical efficacy of EPO dosage adjustment protocol, treatment duration from the initial dose of EPO to the targeted Hb at 10-12 g/dl on 3 consecutive visits was determined. To evaluate the safety of this regimen, adverse reactions were evaluated at every visits. Blood pressure and mean arterial pressure were also determined.

Results

Twelve patients were included in this study. But only nine patients completed the study follow up period Two patients were died from peptic ulcer perforation and cellulitis with septic shock and 1 patient was loss to follow up.

Table 2 Demographic data

Demographic data	CKD stage IV (5)	CKD stage V (4)	total (9)
Male	3	1	4
Age (Mean±Sd; year)	74.60 ± 5.68	60.00 ± 4.24	68.11 ± 9.06
Body weight (Mean±Sd; Kg)	48.20 ± 10.18	54.62 ± 10.40	51.06 ± 10.19
Mean arterial pressure (Mean±Sd; mmHg)	94.75 ± 8.08	87.54 ± 6.97	90.74 ± 7.95
KDQOL-SFTM score (Mean±Sd)	53.26 ± 3.51	56.13 ± 8.75	54.54 ± 6.10
Serum creatinine (Mean±Sd; mg/dl)	5.03 ± 1.71	2.54 ± 0.45	3.65 ± 1.71
eGFR (Mean±Sd; ml/min/1.73 m2)	9.91 ± 3.16	22.07 ± 6.78	16.66 ± 8.24
Intact parathyroid hormone level	68.13 ± 25.3	224.90 ± 96.96	137.80 ± 102.96

Table 2 Demographic data (continue)

Demographic data	CKD stage IV (5)	CKD stage V (4)	total (9)
(Mean±Sd; pg/ml) (normal 16-62 pg/ml)			
Mean transferrin saturation (%)	30.40 ± 10.11	31.50 ± 10.41	30.89 ± 9.60
Mean ferritin (Mean±Sd; ng/dl)	410.24 ± 218.29	516.1 ± 167.06	457.29 ± 193.40
Hemoglobin (Mean±Sd; g/dl)	9.06 ± 0.83	8.37 ± 0.75	8.76 ± 0.83
Hematocrit (Mean±Sd; %)	27.00 ± 2.00	25.50 ± 1.91	26.33 ± 2.00
Comorbidity (number)			
Diabetes	4	2	6
Hypertension	5	4	9

eGFR, estimated glomerular filtration rate; KDQOL-SF™, Kidney Disease and Quality of Life Short-FromTM Questionnaire Version 1.3

Nine patients (4 men and 5 women) were analyzed in this study. Five patients had CKD stage 4. Mean patients' age was 68.11±9.11 years and the average body weight was 51.06±10.19 kg. All patients had hypertension and 6 of them had type 2 diabetes mellitus (table 2).

Hematological response

All nine patients' hemoglobin and hematocrit level were increased after EPO therapies (table 3). The mean duration of treatment to maintain hemoglobin target aforementioned was 112.33±45.11 days (table 4).

Epoietin alfa dose

The mean dose of EPO was 15,555.56±3,711.84 units/month. The mean dose of EPO in patients with CKD stage 4 (14,400±3,577.71 units/month) was lower than that of patients with CKD stage 5 as expected. (17,000 ± 3,829.71 units/month) (table 3).

Blood pressure change

Mean arterial blood pressures during follow up periods were increased in 5 patients (6.25 ± 6.87 mmHg) and decreased in four patients (6.83 ± 2.89 mmHg) (table 5).

Quality of life improvement

All nine patients'quality of life by KDQOL-SF™ Version 1.3 score were improved after 24 weeks evaluation (table 6).

Adverse events and abnormal responses

During EPO administration, any adverse events such as headache, dizziness, rash, fever etc. were not reported.

Table 3 Hematological change

Patient No.	Baseline Hb (g/dl)	End point Hb (g/dl)	Hb change (g/dl)	Duration (weeks)	% change/week (%)
1	8.00	10.10	2.10	17.71	1.48
2	9.50	11.67	2.17	13.00	1.76
3	8.00	10.00	2.00	20.86	1.20
4	8.00	11.00	3.00	6.29	5.96
5	7.90	10.13	2.23	26.00	1.09
6	8.70	11.37	2.67	11.00	2.79
7	9.90	11.07	1.17	23.57	0.50
8	9.80	11.93	2.13	12.00	1.81
9	9.00	10.33	1.33	14.00	1.06
Total (mean±Sd)	8.76±0.83	10.84±0.73	2.09±0.57	16.05±6.44	1.96±1.63

Hb, Hemoglobin

Table 4 Erythropoietin (EPO) dose and duration

	CKD stage IV (5)	CKD stage V (4)	Total
Duration of EPO treatment (days)	121.20±48.71	101.25±44.36	112.33±45.11
Dosage of EPO (units/month)	14400±3577.71	17000±3829.71	15555.56±3711.84

Table 5 Blood pressure change

Patient No.	Baseline MAP (mmHg)	End point MAP (mmHg)	MAP change (mmHg)
1	92.3	94.37	↑2.07
2	84.7	85.15	↑0.45
3	103.3	93.3	↓10.00
4	98.7	91.3	↓7.40
5	85.7	94.08	↑8.38
6	87	90	↑3.00
7	80	97.33	↑17.33
8	86	79.5	↓6.50
9	99	96	↓3.00

MAP, Mean arterial pressure

Table 6 Quality of life by KDQOL SF™ change

Patient No.	Baseline KDQOL-SF™ (0-100)	End point KDQOL-SF™ (0-100)	% Change
1	65.50	69.67	6.37
2	50.93	57.19	12.29
3	61.34	66.77	8.85
4	46.76	54.40	16.34
5	52.69	57.93	9.94
6	59.25	65.50	10.55
7	50.51	60.08	18.95
8	52.88	58.10	9.87
9	50.97	55.31	8.51
Total (mean±Sd)	54.54 ± 6.10	60.55 ± 5.43	11.30 ± 3.99

KDQOL-SF™, Kidney Disease and Quality of Life Short-FromTM Questionnaire Version 1.3

Discussion

Anemia in chronic kidney disease patients had a significant impact on morbidity, mortality and quality of life (QOL). It is primarily a consequence of inadequate erythropoietin production by the kidneys. Therefore, many clinical practice guidelines have been issued to recommend the EPO therapy for treatment of anemia in CKD patients[5]. rHuEPO is rather safe and effective for reducing the risk of cardiovascular disease and improve clinical outcomes in patients with CKD[17]. In our study, EPO dosage adjustment protocol was successfully used to improve clinical practice in renal anemia problem at CKD outpatient clinic.

After treatment, all nine patients had increased in hemoglobin and hematocrit level with the average duration of four months to reach the hemoglobin target which is less than prior randomized controlled trial that required 6 to 9 months[18].

Current clinical practice guideline has suggested the clinician to reevaluate the ferritin level if the patients had no or suboptimal response to EPO therapy[19]. However, there were no patient who had suboptimal response to EPO therapy in our study.

According to the National Kidney Foundation-Kidney Disease Outcomes Qualitative (K-DOQI) anemia guidelines, administration of sufficient iron to maintain the transferrin saturation (TSAT) of >20% and serum ferritin >100 ng/ml were suggested[5]. In this study, all patients were supplemented with ferrous fumarate (at least 200 mg/day) in with no diet restriction, which is our unit routine practice. Routine evaluation of TSAT and serum ferritin in our clinic may not be cost effective.

Interestingly, not only laboratory parameter improvement, general condition and quality of life of the patients in this study were also improved after 24 weeks evaluation. The functional status, appetite, well-being, and symptoms of easily fatigued and dizziness showed significant improvement after the treatment. These may be related to the improvement of anemia or additional effects of erythropoietin itself[3].

Giving EPO may give risen in blood pressure level[20]. The exact mechanism is still controversial, but possibly related to nitric oxide and impairment of endothelial function[20]. In our study, mean arterial pressure (MAP) before and after the treatment were compared, with 5 patients having increases in MAP and 4 patients having decreases in MAP. This adverse effect should be noted and observed for wider use.

Adverse effects including rash, nausea, vomiting and dizziness were not observed in the presented patients. In addition, pure red cell aplasia[21] which has not been found in our study can explained by short period of study and small sample size.

In summary, we developed erythropoietin dosage adjustment protocol for the treatment of anemia in patients with non-dialysis-dependent CKD stage 4 and 5. We found that the mean duration and optimal doses of EPO to maintain targeted hemoglobin at 10-12 g/dl were 112 days and 15,555 units monthly. Adverse effects were not shown in our study. Limitation was small sample size and short followed up period. Long-term side effects should be monitored for long term clinical efficacy and adverse events.

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