The Serum Erythropoietin Level in Patients with Chronic Kidney Disease

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Objective: The erythropoietin (EPO) is well-known synthesized by the kidney. When the function of the kidney is severely impaired, the EPO is expected to decrease. This paper is aimed to quantify the serum EPO in cases of chronic kidney disease (CKD) and to compare it with that of thalassemia major and of the normal control. **Patients and Method:** The serum EPO of newly diagnosed CKD was quantified, compared and analyzed with that of thalassemia major (TM) and of normal people, using Kruskal-Wallis test. **Results:** There were 45 cases per group. The means of EPO level of the CKD, TM and normal groups were 26.4±30.9, 106.2±48.9 and 21.2±27.8 mcg/dl respectively. The EPO of the CKD was similar to that of the normal group but significantly lower than that of the TM group. Every case of TM had the EPO level more than the normal range, and 22 of them had EPO >200 mcg/dl (48.9 %). Ten from the CKD group (22.2 %) and six from the normal group (13.3 %) had the EPO level more than the normal range. **Conclusion:** The serum EPO of CKD, TM and normal groups were 26.4±30.9, 106.2±48.9 and 21.2±27.8 mcg/dl respectively. The EPO level of the CKD was similar to that of the normal but significantly lower than that of the TM group.

Key words: erythropoietin, chronic kidney disease, thalassemia major

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บทคัดย่อ: ระดับ erythropoietin ในเลือดของผู้ป่วยโรคไตเรื้อรัง

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Erythropoietin (EPO) ส่วนใหญ่สังเคราะห์ได้จากไต ในผู้ป่วยโรคไตระยะสุดท้ายจึงคาดว่า EPO น่าจะต่ำ **วัตถุประสงค์:** ต้องการตรวจระดับ EPO ในผู้ป่วยโรคไตเรื้อรัง และเปรียบเทียบกับระดับ EPO ของคนปกติ และผู้ป่วย thalassemia major (TM) **ผู้ป่วยและวิธีการ:** ตรวจระดับ EPO ของผู้ป่วยใหม่ที่ได้รับการยืนยันว่าเป็นโรคไตเรื้อรัง ด้วยเครื่องสะท้อนคลื่นเสียงความถี่สูง หรือเอกซเรย์ คอมพิวเตอร์ ก่อนการเติมเลือด หรือล้างไต เปรียบเทียบกับของคนปกติ และ ของผู้ป่วย TM โดย Kruskal-Wallis test และถ้าค่า p น้อยกว่า 0.05 จะถือว่ามีความต่างกันอย่างมีนัยสำคัญทางสถิติ **ผลการศึกษา:** ผู้ป่วยกลุ่มละ 45 ราย ค่าเฉลี่ยของ EPO ของผู้ป่วยโรคไตเรื้อรังคือ 26.4+30.9 ของกลุ่ม TM และของคนปกติ คือ 106.2+48.9 และ 21.2+27.8 ไมโครกรัม/เดซิลิตรตามลำดับ (ค่าปกติ 2.6-34) ไม่มีความแตกต่าง ระหว่างค่าเฉลี่ย EPO ของกลุ่มโรคไตเรื้อรังและของคนปกติ แต่ของผู้ป่วย TM มีค่ามากกว่าของทั้ง 2 กลุ่มอย่างมีนัยสำคัญทางสถิติ ผู้ป่วย TM มีค่า EPO มากกว่าพิสัยปกติทุกราย โดยมีผู้ที่มีค่ามากกว่า 200 ไมโครกรัม/เดซิลิตร 22 ราย (ร้อยละ 48.9) ในกลุ่มโรคไตเรื้อรัง มีผู้ที่มี EPO มากกว่าพิสัยปกติ 10 ราย (ร้อยละ 22.2) ในกลุ่มคนปกติ มีค่า EPO มากกว่าเกณฑ์ปกติ 6 ราย (ร้อยละ 13.3) **สรุป:** EPO ของกลุ่มโรคไตเรื้อรัง, TM และคนปกติ คือ 26.4+30.9, 106.2+48.9 และ 21.2+27.8 ไมโครกรัม/เดซิลิตรตามลำดับ (ปกติ 2.6-34) ไม่มีความแตกต่างระหว่างค่าเฉลี่ย EPO ของกลุ่มโรคไตเรื้อรังและของคนปกติ แต่ของผู้ป่วย TM มีค่ามากกว่าของทั้ง 2 กลุ่มอย่างมีนัยสำคัญทางสถิติ

Introduction

Erythropoietin (EPO) is a glycoprotein growth factor. Its main function is to enhance the growth and the differentiation of the erythroid progenitors to be normoblast[1]. In the adult, the majority of EPO (about 90 %) is produced in type I fibroblastic cells in the peritubular interstitium of the kidney[2], only small amount of EPO is produced by the liver[3]. Its serum level is in the range of 5-36 mcg/dL which is enough for maintaining the normal hemoglobin (Hb) concentration. The production of EPO is regulated via the feedback mechanisms involving tissue oxygenation. Decreased oxygen delivery, most often due to anemia, is the primary stimulus for EPO release[4], leading to the raised serum EPO. On the other hand, the serum EPO is decreased in the primary polycythemia[5]. When the kidney function is impaired, ie, glomerular filtration rate (GFR) less than 60 ml/1.73 m^2/minute, the production of EPO is decreased[6, 7]. And if such impairment is severe and persistent for 6 months or more, anemia is inevitable. The degree of anemia is moderately to markedly severe and the red blood cell (RBC) morphology is normochromic normocytic. The anemia can be very much improved by the administration of the EPO along with regular dialysis or kidney transplantation.

The serum EPO level in the patients with chronic kidney disease (CKD) has been studied and found controversial, viz, it is decreased[8], normal[9] or even increased[10] without undoubted explanation. Besides the

fact that the kidney is not the sole organ that produces the EPO, furthermore, in case of response to the episodes of spontaneous acute hypoxic stress, EPO level can be tenfold higher than the level during the stable steady state of chronic renal failure[11]. The aim of this paper was to find the serum level of EPO in cases of definite CKD in Thais whether the EPO is lower, normal or higher thal normal level.

Patients and Methods

The patients in medical wards who were newly diagnosed as CKD, were recruited. All of them had serum creatinine level of 10 mg/dL more or less, and the calculated GFR less than 10 ml/minute. And the ultrasonography or the computerized tomography of the upper abdomen was performed to demonstrate both kidneys were contracted in every case. Some of them had history of diabetes mellitus. The other laboratory tests were also simultaneously performed, i.e., CBC, BUN, FBS, liver function test and the electrolytes. Their serum EPO before blood transfusion, dialysis and EPO injection was investigated.

The patients who had the obstructive uropathy demonstrated by the ultrasonography and/or the computerized tomography were excluded. All patients must be more than 20 years of age, they must be conscious to sign the informed consent. The exclusion criteria were chronic liver disease, acute renal failure, primary or secondary polycythemia, pregnancy and microcytic anemia because of the suspicion of the iron deficiency anemia or thalassemia/hemoglobinopathy.

There were 2 control groups, the first was the normal group, ie, their physical examination and laboratory tests including CBC, Hb electrophoresis and creatinine must be normal. The second was the positive control group that consisted of the patients with thalassemia major (TM) who regularly attended hematology clinic for the blood transfusion. All of them were proved to be TM with Hb electrophoresis and all must have normal serum creatinine level and no cirrhosis.

The majority of them were beta-thalassemia/Hb E. Their serum EPO was investigated prior blood transfusion. The serum EPO levels from the 3 groups were compared and analyzed with the Kruskal-Wallis test. If it was demonstrated to be significantly different, the further test was performed to find the different pairs. The *p*-value less than 0.05 would be considered different with statistic significance.

This cross-sectional study was approved by the ethical committee of the hospital, the certificate number was 034/2010. The sample size was calculated to be approximately 42.7 or 45 per group, according to the formula: $N/group = 2(Z_{\alpha}+Z_{\beta})^2 p(1-p)/(P_T-P_C)^2$, presuming that the percentage of low EPO level in CKD was 70[12] while that of the normal people was 35 %.

Results

Forty-five patients with CKD without chronic liver disease were recruited and they consisted of 25 males and 20 females. Ages ranged between 20 and 80 years with mean age 59.9±14.3 years. The other 2 groups had also 45 participants per group. The general demographic data of the participants from 3 different groups were shown in the table 1.

The creatinine level in CKD group ranged from 6.5 to 18.3, mean 11.0±3.0 mg/dL, the calculated GFR was shown to be less than 10 ml/min in every case. And in the other 2 groups, the creatinine levels were normal.

Table 1 The demographic characteristics of the patients with chronic kidney disease (CKD), with thalassemia major (TM) and of normal individuals.

	CKD	TM	Normal
Number	45	45	45
Male	25	22	24
Female	20	23	21
Age range (yrs)	20-80	20-67	20-77
Mean age (yrs)	59.9±14.3	38.5±14.6	48.9±15.2
Creatinine range (mg/dL)	6.5-18.3	0.5-1.1	0.6-1.4
Mean creatinine (mg/dL)	11.0±3.0	0.8±0.2	0.9±0.2
Hb range (g/dL)	3.3-10.5	2.3-9.3	12.0-15.2
Mean Hb (g/dL)	7.8±1.6	6.7±1.7	13.3±0.9
GOT	9.0-86.0	14.0-94.0	13.0-90.0
Mean	33.8±20.8	48.2±22.7	29.5±21.2
GPT	3.0-89.0	11.0-111.0	9.0-125.0
Mean	30.5±24.3	45.0±28.6	26.0±26.3
Albumin (g/dL)	3.0-4.2	3.0-4.5	3.7-4.6
Mean (g/dL)	3.5±0.4	4.0±0.4	4.0±0.2
Globulin (g/dL)	1.5-5.2	2.5-6.8	2.7-5.1
Mean (g/dL)	3.8±0.8	4.0±1.0	3.5±0.6

The means of the Hb concentration of the CKD, the TM and the normal groups were 7.8±1.6, 6.7±1.7 and 13.3±0.9 g/dL respectively. With ANOVA test, there was the significant difference among these 3 means, F value 316.8, *p*-value 0.00. The first two means were in anemic range and by student-T test, and they were not different from each other, *p*-value 0.13. Both means were totally different from the mean of 13.3±0.9 g/dL of the normal group (*p*-value 0.0).

In TM group, GOT and GPT were slightly elevated as compared with those of the CKD and the normal groups.

The serum albumin and globulin looked similar among 3 groups.

The range and mean of the serum EPO level of the patients with CKD, with TM and of the normal individuals were shown in the table 2.

For the TM group, 22 of 45 patients (48.9%) had EPO level more than 200 mcg/dL while the rest (51.1 %) had the serum EPO ranging from 42.9 to 196, mean of 106.2±48.9 mcg/dL which was used to compare and analyze with those of the other groups.

The CKD, the TM and the normal groups had ranges of the serum EPO between 2.6 - 165, 42.9 - 196 and 4.3-192 mcg/dL respectively and had means of 26.4±30.9, 106.2±48.9 and 21.2±27.8 mcg/dL respectively. With Kolmogorov-Smirnov test, all 3 series of data were shown to have the skewness therefore they were analysed and compared with Kruskal-Wallis test and the difference of the serum EPO with statistic significance ($p<0.01$) among 3 groups was verified. When the further tests were performed to find the

Table 2 The serum level of EPO of the patients with chronic kidney disease (CKD), with thalassemia major (TM) and of the normal individuals (normal level 2.6-34 mcg/dL)

	CKD	TM	Normal
EPO (mcg/dL)			
Min	2.6	42.9	4.3
Max	165	196	192
Mean±SD	26.4±30.9	106.2±48.9	21.2±27.8

different pairs, it was found that the EPO of the CKD was similar to that of the normal group (mean difference -5.2, *p*-value 0.76, 95% CI -19.6, 9.2) but different from that of the TM group with statistic significance (mean difference -77.3, *p*-value <0.01, 95% CI -103.9, -50.9) and the EPO of the normal was also different from that of the TM group with statistic significance (mean difference -82.5, *p*-value <0.01, 95% CI -108.6, -56.4). The proportion of the patients in the CKD group who had the EPO level more than the upper limit of the normal range (2.6-34 mcg/L), was 10 out of 45 (22.2%), as compared with 6 of 45 of the normal group (13.3 %). And every case in the TM group had EPO level more than the normal range. No one among 3 groups had EPO level less than the lower limit of the normal range.

Discussion

The range and mean of the serum EPO level in the patients with CKD were 2.6-165 and 26.4±30.9 mcg/dL respectively which were closely similar to the range of 4.3-192 and the mean of 21.2±27.8 mcg/dL of the normal group. More over the proportion of the patients who had serum EPO above the normal range in the CKD group was more than that of the normal group (22.2 % vs. 13.3 %, *p*-value 0.0). None of CKD group had EPO level less than the normal range. These findings confirm the report from Japan that the EPO level in cases of CRF is similar to that of normal individuals, moreover its level can be increased in response to acute blood loss or sudden decrease of oxygen in the arterial blood[9]. These may be explained from the fact that the source of EPO is not only the kidney[2] but also the liver[13], and if the patients have CKD combined with cirrhosis, the decrease of EPO is proved to be more predominant[14] than in CKD alone.

In general, when the people have anemia, the anemic hypoxic drive will stimulate EPO release to increase compensatory erythropoiesis as seen the cases of TM or thalassemia intermedia[15,16]. All patients in the CKD group in our study had moderate degree of normochromic normocytic anemia which fell within the same range of anemia found in the TM group but their severely impaired kidney failed to increase EPO production, as compared with that of the TM group who all had the intact kidneys, in response to hypoxic drive due to anemia.

Besides the relatively lower level than the expectation of the serum EPO, other factors which may aggravate the degree of anemia in CKD group, are the shortening of the RBC survival when they circulate in the uremic plasma, secondary hyperparathyroidism, chronic blood loss, iron deficiency anemia, medical vampirism, etc. These may induce the increased EPO released from other sources such as liver and also it may be the possible explanation why the EPO level in CKD group is normal in the majority and is increased in 22.2% of cases, as found in other study[17], in stead of truly lowered EPO level.

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