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The impact of human recombinant erythropoietin on renal function in patients with chronic kidney disease

Mohamad Reza Tamadon [1], Ahmad Khatibinezhad [1], Raheb Ghorbani [2], Alireza Soleimani [3], Farhad Malek [1], Mojgan Jalalzadeh [4], Mojtaba Malek [5*]

[1] Department of Internal Medicine, Semnan University of Medical Sciences, Semnan, IR Iran
[2] Department of Social Medicine, Semnan University of Medical Sciences, Semnan, IR Iran
[3] Department of Internal Medicine, Kashan University of Medical, Kashan, IR Iran
[4] Department of Internal Medicine, Zanjan University of Medical Sciences, Zanjan, IR Iran
[5] Endocrine research center (Firozgar), Institute of Endocrinology and Metabolism, Tehran University of Medical Sciences, Tehran, IR Iran

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ABSTRACT

Background: Chronic kidney disease (CKD) is a worldwide health problem. But despite to new routes of dialysis, mortality and morbidity is high. One of the most common symptom of CKD is anemia, especially is more obvious in stages 3 and 4.
Objectives: In this study, the effects of erythropoietin on renal function were assessed by measurement of serum creatinine level.
Patients and Methods: Twenty three adult patients with CKD in the stages 3 and 4, enrolled in study and serum creatinine level was monthly measured three months before need to prescribe the erythropoietin due to anemia resulting from CKD (hemoglobin less than 12g/dl) and continued 6 months after administration of the drug. Based on patients' needs, the drug was administered subcutaneously in a dose of 4000-6000 units per week so patients' hemoglobin level became more than 12g/dL. During the study, all patients who required to dialysis or kidney transplantation were excluded from the study
Results: Mean of creatinine and 1/creatinine values in 4 stages including three-month before intervention, time to intervention, and the three months after the intervention and the six month after the intervention were 2.17 and 0.50; 2.45 and 0.45; 2.41 and 0.47; 2.30 and 0.49 respectively which were not statistically significant.
Conclusion: The administration of recombinant human erythropoietin in stage 3 and 4 of chronic kidney disease, improves anemia with no impact on renal function.

Implication for health policy/practice/research/medical education:
A gradual decrease in the progress of renal failure and a lag phase in the response of renal replacement therapies are highly considered by both physicians and researchers in the field. This article tries to emphasize the role of recombinant erythropoietin on renal function and treatment of anemia.

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Background

Chronic kidney disease (CKD) is a serious problem in the general population. There is a growing trend in prevalence and incidence of renal failure in the United States (1). Annual increase in incidence of end stage renal disease (ESRD) resulted in increasing the number of patients who received kidney transplantation, which was increased survival rate of patients. Despite efforts for treating the ESRD and improvement of dialysis quality, still the disease have high mortality and morbidity, and 1, 2 and 5 years survival rate after dialysis have been reported in these patients 81, 65, 34 percent respectively (2). By initiation of different stages of chronic kidney disease (CKD) which resulting from decreasing of renal function, some complications such as uremia, increased of volume, electrolyte disorders and anemia appear and maybe health threatening and can even lead to death if are not properly treated. In other word the main cause of

* *Corresponding author at:* Mojtaba Malek, Tehran University of Medical Sciences, Firozgar Endocrine Research Center, Institute of Endocrinology and Metabolism, Tehran University of Medical Sciences, Tehran, IR Iran. Tel: +98-2188945172, Fax: +98-2188945173.
E-mail address: malekmoj@tums.ac.ir

replacement therapy (dialysis or kidney transplantation) is inability in treating of renal failure complications by drug therapy (3). One of the most important complications of chronic kidney disease is anemia. Production of red blood cells in the bone marrow controlled by erythropoietin, a glycoprotein hormone which secreted from capillary epithelial cells around the renal tubules; also a few amounts of erythropoietin are produced in liver cells (4).

In the absence of erythropoietin, precursor cells of red blood cells in bone marrow are destroyed (Apoptosis). By loss of tissue around the kidney tubules and its failure, amount of erythropoietin reduced and anemia occurs (4). In several studies which done so far, it was not concluded that treatment of anemia caused by CKD with recombinant human erythropoietin could improved the renal function and reduced need to dialysis (3, 5). Some study on rats showed that treatment of anemia due to CKD resulted in more glomeruli damages and exacerbation of hypertension (6, 7). In some studies recommended that for better and true conclusion about effect of erythropoietin on renal function need to more studies (5, 8). The aim of this study was assessment of recombinant human erythropoietin effect on renal function in patients with CKD.

Patients and Methods

In a clinical trial (Before-After), totally 25 adult patients with anemia resulting from chronic kidney disease in stage 3 and 4 (4) (hemoglobin less than 12 g/dl) who referred to our clinic (Semnan-Iran) from May 2008 to October 2009 enrolled in study. Prescription of erythropoietin was 4000-6000 units/week (50-100u/kg/week) based on patients' need to preserve the patients' hemoglobin above 12g/dl. Blood pressure in patients with chronic kidney disease preserved less than 140/90 by antihypertensive drugs including angiotensin converting inhibitors. Other therapies for patients, such as control of diabetes, electrolyte disorders, diet and infections control continued separately as possible. Renal function measured by serum creatinine level. Decreasing of renal function is associated with increased the serum creatinine level, thus we used 1/Cr value for consistency and rational curve of serum creatinine level (9, 10). Serum creatinine level measured with MAN kits and hemoglobin by Culter ABX Micros 60 devices. In the first step of study, three months before intervention the serum creatinine level measured monthly and then 1/Cr value was recorded in curve. In the second step, after administration of EPO, serum creatinine levels were checked monthly for 6 months. The 1/Cr value in respect to the mean value of serum creatinine levels recorded in a curve and decreasing of mean creatinine levels (as 1/Cr value) were compared in the first and second stages. In this study, the patients who need to dialysis or renal transplantation for any reason were excluded from the study. All patients filled an informed consent and all data kept confidential and only used for collective analysis. Paired t-tests and repeated measurement in significant level of 5% used for statistical analysis.

Results

Two patients excluded from study because of poor cooperation. From 23 patients fulfilled the study, 14 patients were female and 9 male (60.8 and 39.2% respectively). Mean (± SD) of patients' age was 62.3 ± 17.4 years. Youngest and oldest patients with CKD had 30 and 88 years old, respectively. Fifteen patients had hypertension and 7 patients had hypertension and also diabetes mellitus. One patient had autosomal dominant polycystic kidney disease; one patient had IgA nephropathy, one patient with systemic lupus erythematosus and causes of CKD in 5 remaining patients were unknown. The mean of Glomerular filtration rate (GFR) in patients just before intervention was 30.3 ± 10.5ml/min/1.73m 2. Ten patients were in 3rd and 13 patients in 4th stage of CKD. Lowest amount of GFR was 18ml/min/1.73m 2 and the highest was 49ml/min/1.73m 2. The mean of fasting blood sugar level in diabetic patients in quarter before intervention was 116mg/dl, and during intervention was 111.7 mg/d, in the first and second quarter after the intervention were 132 mg/dl and 125mg/dl respectively which were not statistically significant. Mean of hemoglobin level was 11.4g/dl just before administration of recombinant human erythropoietin and 12.3g/dl during 3 months before the intervention and 12.6 and 12.9 g/dl in the first and second quarter after the intervention respectively *(Table 1)*. The mean of serum creatinine level and its 1/Cr value were calculated in nine times (monthly) which drawn as figures 1 and 2 and showed in *Tables 2*. Mean creatinine level in 4 stages including three-month before intervention, time to intervention, the first three months after the intervention and the second quarter after the intervention was not statistically significant ($p = 0.055$, $F(3, 66) = 2.701$). Also, mean of 1/Cr value in mentioned periods were not statistically significant ($p = 0.107$ and $F(3, 66) = 24.493$).

Table 1. Mean, standard deviation, minimum and Maximum of hemoglobin level measured monthly

Time of measurement	Hemoglobin level g/dl			
	Mean	SD	Minimum	Maximum
3 Months Before Intervention	12.4	0.36	12	13.2
2 Months Before Intervention	12.4	0.43	12	13.6
1 Months Before Intervention	12.3	0.26	12	13
Initiating of Intervention	11.4	0.50	9.8	11.9
1 Month After Intervention	12.4	0.96	11	14.5
2 Months After Intervention	12.8	0.80	11	14.2
3 Months After Intervention	12.8	0.65	11.8	14.6
4 Months After Intervention	13	1.03	11.2	14.8
5 Months After Intervention	13.1	0.98	11.4	15.6
6 Months After Intervention	12.8	1.08	11.5	15.6

Discussion

In our study, results showed that mean of creatinine level and mean of 1/Cr value creatinine level in ten time monthly measurements (three months before and six months after intervention) and also in four three-month period included

Table 2. Mean, standard deviation of creatinine level and its 1/Cr value in different periods before and after intervention

Time of measurement	Serum Creatinine level mg/dl					1/Cr value				
	Mean	SD	Minimum	Maximum	p-value	Mean	SD	Minimum	Maximum	p-value
3 Months Before Intervention	2.17	0.69	1.40	4	0.055	0.50	0.13	0.13	0.25	0.107
2 Months Before Intervention	2.21	0.63	1.50	3.90	0.055	0.48	0.12	0.26	0.67	0.107
1 Month Before Intervention	2.32	0.81	1.50	4.20	0.055	0.47	0.13	0.24	0.67	0.107
Initiating of Intervention	2.45	0.74	1.40	3.80	0.055	0.45	0.13	0.26	0.71	0.107
1 Month After Intervention	2.41	0.83	1.10	4.20	0.055	0.47	0.17	0.24	0.91	0.107
2 Months After Intervention	2.55	0.85	1.10	3.90	0.055	0.44	0.17	0.26	0.91	0.107
3 Months After Intervention	2.34	0.75	1.50	3.90	0.055	0.47	0.15	0.26	0.67	0.107
4 Months After Intervention	2.26	0.75	0.90	3.90	0.055	0.50	0.19	0.26	1.11	0.107
5 Months After Intervention	2.16	0.71	0.90	3.30	0.055	0.52	0.20	0.30	1.11	0.107
6 Months After Intervention	2.30	0.78	0.91	3.90	0.055	0.49	0.20	0.26	1.11	0.107

three-month period before intervention, time of intervention, the first and second quarter after intervention were not statistically significant. Studies so far carried out on humans, including Lim and colleagues who studied the effect of erythropoietin in 26 patients with chronic kidney disease, concluded that neither administration of erythropoietin nor normal hematocrit level reduced renal function significantly (11). Roth and colleagues find that the treatment of anemia in patients with renal failure and so that hematocrit level reaches to normal range, has not any effect on residual renal function (12). Rossert J and colleagues find that normalizing the hemoglobin levels by recombinant human erythropoietin in patients with chronic kidney disease would not increased rate of renal function reduction than correction of severe anemia (8). Mentioned studies have findings and results similar to our study.

Several studies, including Tapolyai M (3), Dean BB and colleagues (5) and Jungers P showed that administration of recombinant human erythropoietin in patients with chronic kidney disease not only does not worsen residual renal function but decreased the rate of renal function reduction. Our study did not showed improvement of renal function or delay in the rate of renal function loss after administration of recombinant human erythropoietin. These differences may be due to genetic effects, differences in the mean age of patients who enrolled in study and duration of the study. Although treatment of anemia as a complication of chronic kidney disease was achieved in late 1980 by access to recombinant human erythropoietin, but this route was delayed with regard to possibility of exacerbation the renal failure. This possibility was based on studies on mice that were implicated in protective role of anemia for nephron, thus improvement of anemia may be exacerbated the renal damage (6, 7). The causes of difference in our results and animal models can be due to this matter that in mentioned studies, antihypertensive drugs including angiotensin converting inhibitors which could reduce glomerular pressure and subsequently prevent injury to nephrons were not prescribed. Our patients who had primary hypertension or secondary to CKD were treated with the above mentioned drugs. Second, in animal model apparent change in hematocrit level from 27 to 51% by erythropoietin could resulting in increasing of the blood viscosity and peripheral vascular resistance and decreasing of capillary blood flow (11). But in our study, the mean Hb levels were preserved between 11 to 13 g/dl. Finally it seems that 83% resection of kidneys in mice and acute changes in blood flow resulted in systemic and glomerular hypertension and subsequently glomerular sclerosis that this phenomenon did not occur or was brief in our patients. In this study we have not any limitation and enrolled all patients with CKD in stages 3 & 4. It seems that the treatment of anemia by recombinant human erythropoietin in chronic kidney disease, when it accompanied by control of metabolic complications, can improve anemia but has not any effect on reduction of renal function rate. For confirming of erythropoietin effect on renal function, we need to a study with larger samples size and longer period of time.

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Conflict of Interest

This study conducted as research project which sponsored by Semnan University of Medical Sciences and didn't receive any financial support from other institutions.

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