World Journal of Pharmaceutical and Life Sciences
WJPLS
www.wjpls.org
SJIF Impact Factor: 5.088

COMPARABLE EFFECT OF DIFFERENT ERYTHROPOIETIN PLASMA LEVELS IN PATIENTS WITH CHRONIC RENAL FAILURE

Hayder Abdulhafedh Kurji*[1], Hayder Al-Anbari[2], Qutaiba Ahmed Ibrahim[3], Fatimah Kadhim Al Mahdawi[4], Mazin Razooqi Mohammed[5] and Nabeel Khalid AL-Wandi[6]

[1]Head of Department/ Faculty of Pharmacy, Bilad Al-Rafidain University College, Iraq.
[2]College of Pharmacy, University of Ahlulbait, Kerbala, Iraq.
[3]Assistant Professor/ Faculty of Pharmacy, Bilad Al-Rafidein University College, Iraq.
[4]Faculty of Pharmacy, Bilad Al-Rafidain University College, Iraq.
[5,6]Consultant Doctors, Baqubah Teaching Hospital, Diyala Health Directorate, Iraq.

***Corresponding Author: Hayder Abdulhafedh Kurji**
Head of Department/ Faculty of Pharmacy, Bilad Al-Rafidain University College, Iraq.

Article Received on 12/07/2019 **Article Revised on 02/08/2019** **Article Accepted on 22/08/2019**

ABSTRACT

Introduction: The kidney is the main site for the synthesis of Erythropoietin, which represents the circulating hormone responsible for stimulatory effect on bone marrow for the erythropoiesis. In case of chronic kidney disease (CKD), Erythropoietin deficiency is the main cause of anemia. Erythropoietin synthesis by DNA technology results in revolution in the management strategies of anemia in CKD. This study aimed to evaluate the effect of different doses (different serum concentration) of erythropoietin on anemia treatment outcome in different stages of renal disease. **Material and methods**: this prospective study was conducted on 245 patients categorized into three groups according to their stage of renal disease. Serum concentration of Erythropoietin, HGB, Transferrin, Ferritine, RBC, and hsCRP were measured using spectrophotometric and immunochemical procedures. **Results**: There was a significant reduction in hematocrit, HGB in patients with advanced stage kidney disease in comparison to early stage p=0.00567, p=0.00533. Transferrin was significantly less in stage V in comparison to early stage of renal disease p=0.00635. Ferritin was significantly higher in stage V comparing to that of early stage of renal disease. Serum concentration of erythropoietin was directly correlated with hematocrit and Hb in early stage of renal disease EP0 R^2 = 0.597 Hct, R^2 = 0.674 HB, whereas, in patients with stage 5 renal disease, erythropoietin is poorly correlated with hematocrit and Hb, EP0 R^2 = 0.05353 Hct R^2 =0.064 HGB. **Conclusion**: Advanced renal failure is associated with lack of erythropoietin and consequently result in severe anemia. The stimulatory effect on bone marrow by erythropoietin is reduced with progression of renal disease.

KEYWORDS: Renal disease, hemoglobin, hematocrit, erythropoietin, and anemia.

INTRODUCTION

Erythropoietin, also known as EPO, is a glycoprotein hormone directly connected to the production and maintenance of red blood cells.[1]

Kidney's fibroblasts and hepatic perisinusoidal cells synthesize erythropoietin in response to cellular hypoxia; it stimulates the bone marrow for red blood cells production through the process of erythropoiesis.[2] For normal red blood cells turnover, average plasma concentration 10 mU/ml of erythropoietin are constantly secreted.[3] Pathological condition causing cellular hypoxia, such as anemia and respiratory disease, resulting in higher level of erythropoietin in plasma up to 10 000 mU/ml.[4]

Erythropoietin has non hematopoietic effects including vasoconstriction, angiogenesis and anti-apoptotic effects that are reported by many clinical studies, although others studies conclude no effect. Additionally, Erythropoietin has been reported to have neuroprotecive effects in diabetic patients.[5]

Erythropoietin-stimulating agents is produced by recombinant DNA technology in cell culture and present in two pharmaceutical products, erythropoietin alpha and erythropoietin beta.[6] These products are indicated for patients with chronic renal disease for treatment of anemia, myelodysplasia with sever anemia, chemotherapy induced anemia and Crohn's disease.[5]

MATERIAL AND METHODS

This survey was conducted on 245 patients categorized into three groups according to their stage of renal disease. Depending on the GFR, third stage renal insufficiency was 94 patients with GFR between 30-59 ml/min/1.73 m^2, fourth stage renal insufficiency was 83 patients with GFR of 15-29 ml/min/1.73 m^2, and 68 patients were at end stage renal disease with less than 15 ml/min/1.73 m.[10] The age groups for the subjects were: stage III was 36.96 ± 8.82, stage IV was 35.66 ± 9.16, and stage V was 34.71 ± 7.92.

GFR for patients were measured by using age, gender and serum creatinine according to the Cockcroft-Gault equation-estimated CCr. Serum concentration of Erythropoietin is measured by enzymatic-chemiluminescent immunometric method, HGB, Transferrin, Ferritine, RBC, and hsCRP were measured using spectrophotometric and immunochemical procedures.

Statistical Analyses

Study's data are expressed by means ± SD. Changes between parameters of different stages of renal failure were assessed by two-way ANOVA. All tests for significance and resulting ***P*** values were two sided, with a level of significance of 0.05. All data analyses were performed with an IBM SPSS version 22.

RESULTS

The characteristics of 245 patients who met the study criteria are shown in table 1. The hematocrit and RBC count were significantly decreased in patients starting creatinine clearance < 29ml/min/1.73 m^2 (stage V) (p =0.00567 and 0.00321). Anemia is significantly observed in advanced renal disease (stage V) and it is directly related to the decline of creatinine clearance in advanced renal failure as observed by HGB (p =0.00533). Transferrin level was significantly less in patients at stage V in comparison to those at stage III and stage IV (p =0.00635). Ferritin was higher in patients with end stage renal disease in comparison to the earlier stage (p = 0.02085). The values of hsCRP were significantly increased with progression of renal disease (p =0.00032), whereas, there are no significant increment in early stage of disease.

There were good correlations between plasma concentrations of EPO with HCT and HGB at early stage of renal disease (EP0 R^2 = 0.597 Hct, R^2 = 0.674 HGB) (figure 1 and 2), whereas, in patients with stage V renal disease, erythropoietin is poorly correlated with hematocrit and Hb, (EP0 R^2 = 0.064 HGB, R^2=0.05353 Hct) (figure 3 and 4).

Table 1: Change in the measured parameters according to the categorized creatinine clearance.

Parameter	Stage III	Stage IV	Stage V	P value
Hematocrit	37.585% ± 5.746	34.386% ± 6.473	24.954% ± 7.673	0.00567
HGB	10.885 ± 1.992	9.786 ± 1.321	9.060 ± 1.016	0.00533
Transferrin	17.906 ± 14.375	2.385± 0.095	2.089 ± 0.593	0.00635
Ferritin	244.883± 138.914	283.862 ±337.343	465.315± 282.712	0.02085
RBC	4.164 ± 0.689	4.103 ± 0.564	3.453 ± 0.456	0.00321
hsCRP	3.874 ± 1.832	3.395 ± 2.045	32.069 ± 31.405	0.00032

Hematocrit ad- hoc: stage III and V, stage IV and V.
HGB ad- hoc: stage III and V.
Transferrin ad- hoc: stage III and IV, stage III and V.
Ferritin ad- hoc: stage III and V.
RBC ad- hoc: stage III and V, stage IV and V.
hsCRP ad- hoc: stage III and V, stage IV and V.

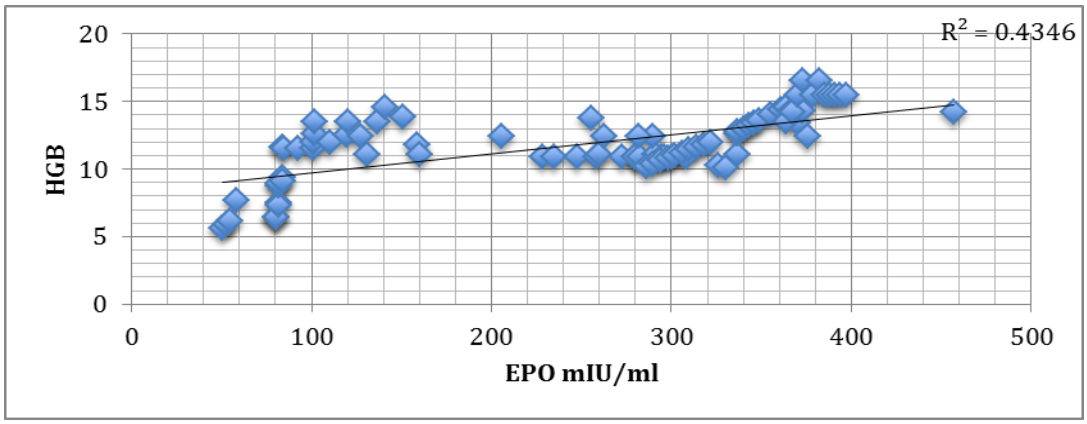

Figure 1: Correlation between EPO plasma concentration and HGB in stage III renal impairment

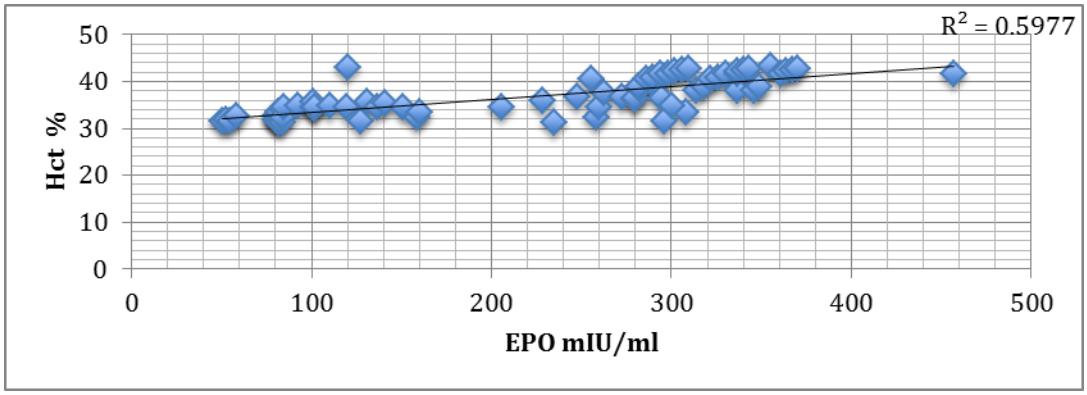

Figure 2: Correlation between EPO plasma concentration and Hct % in stage III renal impairment.

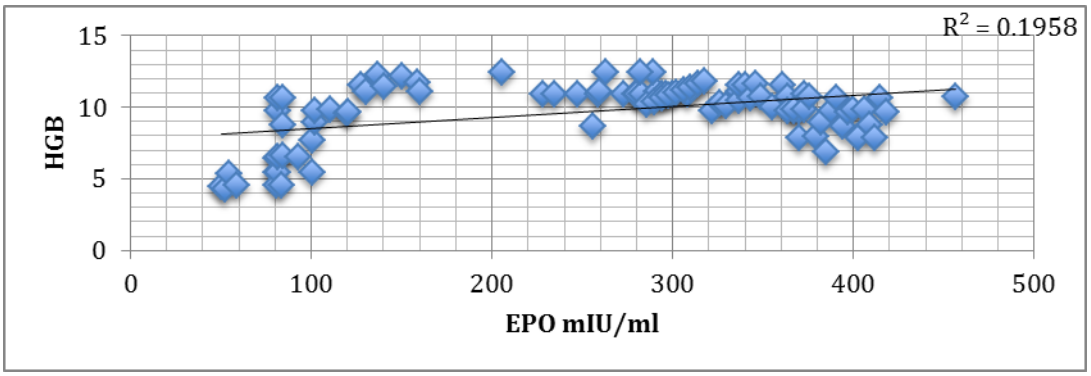

Figure 3: Correlation between EPO plasma concentration and HGB in stage V renal impairment.

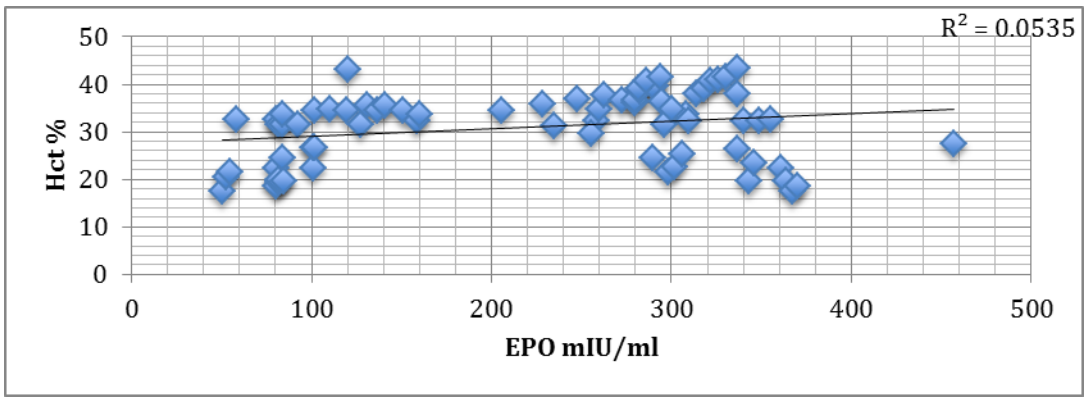

Figure 4: Correlation between EPO plasma concentration and Hct % in stage V renal impairment.

DISCUSSION

Anemia is the most frequent complication of renal disease and it progressed during the advanced stage of chronic renal impairment. The pathophysiology of anemia is complex and may be associated with many factors such as iron deficiency, but the main etiology is the erythropoietin deficiency. Anemia in chronic kidney diseases was associated with fatigue and shortness of breathing.

Effective erythropoiesis is dependent on the availability of adequate iron and erythropoietin. In kidney disease, iron is deficit due to the reduction in gastrointestinal absorption and reduced releasing of stored in the body.[7]

In this study we aimed to evaluate the effect of erythropoietin in advanced chronic renal disease and its effect on treating anemia.

Our study indicate that anemia is progressed in association with the advanced renal disease as illustrated by significant reduction in hematocrit, RBC count, HGB, Ferritin and Transferrin in relation to reduction in creatinine clearance as indicator for renal impairment staging. Additionally, hsCRP, the predictor of cardiovascular disease and other associated oxidative stress resulting consequences, was increased with advanced renal impairment. The efficacy of erythropoietin was decreased with progression of renal disease as confirmed by poor correlation between the concentration of EPO with HGB and Hct in patients with end stage renal disease as comparison to the earlier stage.

The study of Akbar et al in 2013 that compare 96 patients with acute and 36 patient with chronic renal failure concluded that Hct, HGB, and RBC count was significantly less with advanced renal disease.[8] Additionally, Anwar et al study in 2017 showed that the RBC count, hemoglobin levels and platelets counts are significantly reduced in the patients of chronic renal failure.[9] The same result confirmed by Cindy et al in 2018, the RBC indices, including RBC count, haematocrit and haemoglobin levels were consistently lower in CKD participants compared with the group with normal kidney function (all $p<0.0001$).[10] These studies were compatible with our study results of lower level of Hct, HGB, and RBC in late stage renal impairment comparing to the earlier stage.

Ferritin is a good measure of body iron status. The study of Przybyszewska et al in 2013 described that in chronic renal failure, serum ferritin level is usually increased as a result of retention of iron by the reticulo-endothelial cells and overproduction as a result of inflammatory response. In their study, 5 fold increasing in ferritin was seen in patients with end stage renal disease. This compatible with our study results of higher level in stage V comparing to stage III.

Transferrin with Ferritin can be used together for determination of iron status in patients with different disease. Low Transferrin may indicate either iron deficiency or excessive erythropoiesis.[11] Most studies have revealed that serum ferritin is very well related with iron stores in the bone marrow is the best surrogate of iron status in healthy individuals.[12] However, ferritin is an acute phase reactant increasing in states of chronic inflammation (such as dialysis), malignancy, or systemic disease, and ferritin levels alone may not reflect iron stores available for haematopoiesis.[13]

Other study suggest that Transferrin could be a good clinical tool to reveal the underlying cause of anemia in early stages in CKD, this study confirm that Transferrin level is low in CKD but it is high in iron deficiency [14]. In our study, the low level of Transferrin was associated with advanced renal disease confirm that.

Although some studies suggest that IL6 may be more predictor than hsCRP for cardiovascular and oxidative stress associated disease secondary to the CKD[15], other studies confirm the productivity of hsCRP as predictor for cardiovascular disease in CKD.[16] The role of hsCRP was very informative in our study about the progression of the renal disease and it is significantly lower in the end stage of disease.

The efficacy of erythropoietin in treating anemia in end stage renal disease was less than in early stage as illustrated by the review of Cody et al 2001.[17] However, other study indicates that the efficacy of erythropoietin was variable and depending on the underlying cause of the anemia.[18]

In our study, the efficacy of erythropoietin was significantly less in patients with end stage renal impairment as confirmed by poor correlation between plasma concentration of EPO with HGB and Hct. This required further investigation to determine the possibility of other associated factors for loss of EPO activity.

CONCLUSION

The progression of chronic renal failure is associated with severe anemia and in the early stage of disease; EPO is more effective than advanced late stage of renal failure.

REFERENCES

1. Yuanyuan Zhang, Li Wang, Soumyadeep Dey, Mawadda Alnaeeli, Sukanya Suresh, Heather Rogers, et al. Erythropoietin Action in Stress Response, Tissue Maintenance and Metabolism. Int J Mol Sci., 2014 Jun; 15(6): 10296–10333.
2. Wolfgang Jelkmann. Regulation of erythropoietin production. J Physiol, 2011 Mar 15; 589(Pt 6): 1251–1258.
3. Steve Elliott and Angus M Sinclair. The effect of erythropoietin on normal and neoplastic cells. Biologics, 2012; 6: 163–189.
4. Mark J. Koury and Volker H. Haase. Anaemia in kidney disease: harnessing hypoxia responses for therapy. Nat Rev Nephrol, 2015 Jul; 11(7): 394–410.
5. Giovanni Grasso Giovanni Tomasello Marcello Noto Concetta Alafaci Francesco Cappell. Erythropoietin for the Treatment of Subarachnoid Hemorrhage: A Feasible Ingredient for a successful Medical Recipe. Molecular Medicine, 2015; 21(1): 979–987.
6. Wolfgang Jelkmann. Recombinant EPO production—points the nephrologist should know. *Nephrology Dialysis Transplantation*, 2007; 22(10): 2749–2753.
7. Steven Fishbane and Bruce Spinowitz. Update on Anemia in ESRD and Earlier Stages of CKD: Core Curriculum 2018. Am J Kidney Dis., 71(3): 423-435. Published online January 11, 2018.
8. Akbar Dorgalaleh, Mohammad Mahmudi, Shadi Tabibian, Zahra Kashani Khatib, Gholam Hossein Tamaddon, Esmaeil Sanei Moghaddam, et al. Anemia and Thrombocytopenia in Acute and Chronic Renal Failure. Int J Hematol Oncol Stem Cell Res., 2013; 7(4): 34–39.
9. Anwar Habib, Razi Ahmad, Sana Rehman. Hematological changes in patients of chronic renal failure and the effect of hemodialysis on these parameters. *Int J Res Med Sci., 2017 Nov; 5(11): 4998-5003.*
10. Cindy George, Tandi E Matsha, Rajiv T Erasmus, Andre P Kengne. Haematological profile of chronic kidney disease in a mixed-ancestry South African population: a cross- sectional study. BMJ Open, 2018; 8: e025694. doi:10.1136/bmjopen-2018-025694

11. Przybyszewska J, Żekanowska E, Kędziora-Kornatowska K, Boinska J, Cichon R, Porzych K. Serum prohepcidin and other iron metabolism parameters in elderly patients with anemia of chronic disease and with iron deficiency anemia. Pol Arch Med Wewn., 2013; 123(3): 10511.
12. Anith Kumar Mambatta, Murali Alagesan, Mohammed Meeran, Joshua L. Rein, Sivaramakrishnan Ganesan, Anil C. Mathew, et al. Evaluation of iron status in patients with end stage renal disease *Int J Adv Med., 2017 Oct; 4(5): 1415-1421*.
13. Ali Rafi, Ayman Karkar, Mohammed Abdelrahman. Monitoring Iron status in End-Stage Renal Disease Patients on Hemodialysis. Saudi J Kidney Dis Transplant, 2007; 18(1): 73-78.
14. Łukaszyk E., Łukaszyk M., Koc-Żórawska E., Tobolczyk J., Bodzenta-Łukaszyk A., Małyszko J. Iron Status and Inflammation in Early Stages of Chronic Kidney Disease. Kidney Blood Press Res., 2015; 40: 366-373.
15. Stenvinkel P, Lindholm B. C-reactive protein in end-stage renal disease: are there reasons to measure it? Blood Purif., 2005; 23(1): 72-8.
16. Sachimi Kubo, Akihiko Kitamura, Hironori Imano, Renzhe Cui, Kazumasa Yamagishi, Mitsumasa Umesawaet al. Serum Albumin and High-Sensitivity C-reactive Protein are Independent Risk Factors of Chronic Kidney Disease in Middle-Aged Japanese Individuals: the Circulatory Risk in Communities Study. J Atheroscler Thromb, 2016; 23(9): 1089–1098.
17. Cody JD, Daly C, Campbell MK, Donaldson C, Grant A, Khan I, et al. Recombinant human erythropoietin for chronic renal failureanaemia in pre-dialysis patients (Review). Cochrane Database of Systematic Reviews, 2001, Issue 4. Art. No.: CD003266.
18. Wallace A.Marsh, Karen L.Rascat. Meta-analyses of the effectiveness of erythropoietin for end-stage renal disease and cancer. Clinical therapeutics, 1999; 21(9): 1443-1455.