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Assessment Of Erythropoietin Efficacy And Dosing In Hemodialysis Patients

Mostafa Fawzy Mohamed Selim[1], Essam Eldin Mahmoud Lotfy[1], Lamiaa Abd Elwahab Mohamed[2], Mahmoud Hosny Zahran[1]

[1]*Internal Medicine Department, Faculty of Medicine, Zagazig University, Zagazig , Egypt.*
[2]*Clinical Pathology Department, Faculty of Medicine, Zagazig University, Zagazig , Egypt.*

Corresponding Author:Name: Mostafa Fawzy Mohamed Selim
Email: mostafaselim945@yahoo.com

Abstract
Background: Anemia is a common complication in Chronic kidney disease (CKD) patients. It has a multi-factorial pathogenesis. Replenishing iron stores and giving ESAs are the main lines of treatment. There is a general agreement on the optimal route for iron supplementation in ESRD patients with the IV route but there is no such agreement on the optimal route for iron supplementation in pre-dialysis CKD patients. Erythropoiesis stimulating agents (ESAs) treatment represent an economic burden and has been linked to possible cardiovascular side effects. This study amid to assessing the efficacy of erythropoietin in treatment of anemia in CKD patients. Methods: A prospective cohort study was conducted in chronic kidney disease patients who had undergone hemodialysis in Met-Ghamr hospital of nephrology from February 2019 to July 2019. Included 50 patients on maintenance hemodialysis, we tested the efficacy through comparing the efficacy low fixed ESA dose (4000 IU IV once weekly) versus high fixed dose (4000 IU IV three times weekly). We divided group into two groups, group A and group B. group A were put on a fixed dose of 4000 IU Epoetin alfa once weekly and group B were put on a fixed dose of 4000 IU Epoetin alfa three times weekly. Results: After 6 months, We found a significant difference in hemoglobin response of the two subgroups in favor of subgroup IID (P = 0.004). Conclusion: That low dose ESAs is less effective in correction of anemia in dialysis patients than high dose ESAs.

Keywords: Erythropoietin stimulating agents, Chronic Kidney Disease, Glomerular Filtration Rate , Anemia, Iron

1. INTRODUCTION

Iron deficiency is a common reversible factor contributing to the development of anemia in CKD patients and can be easily treated[1].

The cornerstone in the treatment of anemia in CKD patients is giving erythropoiesis stimulating agents (ESAs) after repletion of iron stores [2] .

Erythropoietin-stimulating agent (ESA) is the main modality for treating anemia in ESRD patients but sufficient iron stores needs to be accomplished first[3].

KDIGO (Kidney Disease: Improving Global Outcomes), NKF-KDOQI (National Kidney Foundation-Kidney Disease Outcomes Quality Initiative) and ERBP (European Renal Best Practice) all recommend iron supplementation in anemic CKD patients with an absolute or functional iron deficiency. However, there is no general agreement between them on the

cutoff levels of transferrin saturation (TSAT) and ferritin for the initiation of iron supplementation[4] .

Although there is an agreement between the guidelines on recommending the specific intravenous route for iron supplementation for CKD patients on hemodialysis therapy (CKD stage 5D), they recommend no particular route for iron supplementation for non-dialysis dependant CKD patients (CKD stages 3:5) [4].

However, even in the initial studies, adverse effects were noted in patients receiving ESAs, including worsening hypertension, seizures, and dialysis access thrombosis [5]. Moreover, target Hemoglobin level remains a controversial topic. National Kidney Foundation Dialysis Outcomes Initiative (KDOQI) guidelines for ESA treatment recommends the upper limit for Hb value to be below 12 g/dl [6]. European Renal Best Practice (ERBP) has the view that Hb levels in CKD patients should be kept around 11-12 g/dl and not intentionally exceeding 13 g/dl [7].

Aim of the work:

This study aims at comparing the efficacy of lower doses of ESAs versus higher doses of ESAs in raising hemoglobin levels in hemodialysis patients.

2. PATIENTS AND METHODS

A prospective study was conducted in Met-Ghamr hospital of nephrology from February 2019 to July 2019. Included 50 chronic kidney disease (CKD) patients who had undergone maintenance hemodialysis, divided equally into two groups, group A and group B. group A was given low fixed dose of an erythropoiesis stimulating agent (ESA). 14 males and 11 females with a mean age of 55.24 (± 15.46). While group B was given a high fixed dose of an ESA. 10 males and 15 females with a mean age of 50.32 (± 10.51). Ethical approval was taken from the ethical clearance committee and verbal consent was taken from all the patients after explanation of the benefits and possible risks of the study. The work has been carried in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsiniki) for studies involving humans.

Inclusion criteria: CKD Patients on hemodialysis with hemoglobin level ≤ 11 gm/dl either using erythropoietin or not. **Exclusion criteria:** Exclusion criteria: Patients with hemoglobin level higher than 11 gm/dl. Patients with macrocytic anemia attributed to folate or vitamin B12 deficiency. Patients who had kidney transplantation. Patients who had blood transfusions within the last three months. Patients with acute or chronic bleeding. Patients with active infection. Patients with malignant disease. Patients with advanced cardiovascular disease. Pregnant or lactating female patients.

All patients were subjected to history taking, Complete physical examination with special emphasis on blood pressure and its control and laboratory. A pre-dialysis specimen were taken directly from vascular access to perform all laboratory investigations. Beside regular tests, Complete blood count, baseline and serial at the 2^{nd}, 4^{th} and 6^{th} months. (by automated blood counter, sysmex XN 2000), their transferrin saturation (TSAT), serum ferritin, iPTH level , Ionized calcium and phosphorus, Serum creatinine and urea.

Serum albumin, TSH level.

A post-dialysis specimen of 2 ml were taken to perform post-dialysis urea (by Cobas 8000 series module C 702) to calculate (URR) urea reduction ratio (target > 65%). the specimen was collected at the completion of hemodialysis, dialysate flow is turned off and the ultrafiltration rate (UFR) decreased to 50ml/hr or turned off. Blood flow decreased to 100 ml/min for 15 seconds. Blood specimens obtained with a syringe from arterial sample port on arterial bloodline.

Regardless of baseline hemoglobin, patients allocated into two groups. Group A: 25 patients were given a fixed epoetin alfa dose of 4000 IU once per week intravenously. Group B: 25 patients were give a fixed epoetin alfa dose of 4000 IU 3 times per week intravenously.
Patients of both groups were followed monthly for compliance and any possible adverse effects. Hemoglobin level were followed up at the 2nd month, 4th month and the 6th month, as patients who are under regular maintenance haemodialysis are not lost to follow-up in such a time interval. During the course of the study, patients was receive their regular additional co-intervention for other co-morbidities in general (IV iron, anti-hypertensive agents, CKD-MBD agents).

3. STATISTICAL ANALYSIS

All data were collected, tabulated and statistically analyzed using SPSS 25.0 for windows (SPSS Inc., Chicago, IL, USA).

4. RESULT

Table (1): Distribution of the demographic characteristics

	Group			
	A (n=25)		***B (n=25)***	
	No.	***%***	***No.***	***%***
Sex				
Male	14	56.0	10	40.0
Female	11	44.0	15	60.0
$^{\square}$p	p_2=0.258			
Age (years)				
Min. – Max.	20.0 – 89.0		26.0 – 70.0	
Mean ± SD.	55.24 ± 15.46		50.32 ± 10.51	
^{t}p	p_2=0.194			

$^{\square}$p: p value for Chi square test *^{t}p: p value for Student t-test*
p_2: p value for comparing between group IIC and group IID

There was no significant difference in the demographic characteristics between the two groups. **Table (1)**

Table (2): Baseline characteristics of group:

	Group	
	A(number=25)	**B (number=25)**
Iron parameters		
TSAT		
Min. – Max.	**22.0 – 89.0**	**24.0 – 76.0**
Median (IQR)	**36.0 (29.50 – 47.50)**	**34.0 (29.50 – 47.50)**
^{U}p	**p_2=0.627**	
Ferritin		
Min. – Max.	**51.0 – 966.0**	**52.0 – 950.**
Median (IQR)	**218.0(126.5–436.5)**	**311.0(139.5 – 469.5)**
^{U}p	**p_2=0.277**	
PTH		
Min. – Max.	**33.0 – 295.0**	**53.0 – 297.0**
Median (IQR)	**187.0 (129.0– 254.5)**	**163.0 (98.0 – 245.5)**
^{U}p	**p_2=0.190**	

Ionized calcium		
Min. – Max.	**1.01 – 1.45**	**0.76 – 1.42**
Mean ± SD.	**1.22 ± 0.13**	**1.16 ± 0.16**
^{t}p	**p_2=0.201**	
Phosphorus		
Min. – Max.	**2.30 – 7.20**	**3.0 – 7.10**
Mean ± SD.	**4.29 ± 1.23**	**4.66 ± 1.18**
^{t}p	**p_2=0.285**	
Albumin		
Min. – Max.	**1.80 – 4.20**	**2.90 – 4.70**
Mean ± SD.	**3.53 ± 0.57**	**3.78 ± 0.39**
^{t}p	**p_2=0.078**	
TSH		
Min. – Max.	**1.38 – 3.14**	**1.31 – 3.02**
Mean ± SD.	**2.31 ± 0.51**	**2.29 ± 0.52**
^{t}p	**p_2=0.898**	
Duration of dialysis		
Min. – Max.	**8.0 – 78.0**	**3.0 – 64.0**
Median (IQR)	**23.0 (18.50 – 47.50)**	**26.0 (11.0 – 35.0)**
^{U}p	**0.541**	
Urea reduction ratio		
Min. – Max.	**68.0 – 96.0**	**67.0 – 87.0**
Mean ± SD.	**73.84 ± 5.81**	**74.40 ± 5.11**
tp	**0.719**	

P_2: p value for comparing between group IIC and group IID
^{U}p: p value for Mann Whitney test ^{t}p: p value for Student t-test

There was no significant difference in the baseline characteristics between the two groups of group 2 (group A and group B) regarding iron parameters, PTH, ionized calcium, phosphorus, albumin, TSH, duration of dialysis and urea reduction ratio. **Table (2)**

Table (3): Distribution of the studied groups according to the cause of CKD:

Cause of CKD	**Group**			
	(A) (n=25)		**(B) (n=25)**	
	No.	**%**	**No.**	**%**
HTN	**12**	**48.0**	**15**	**60.0**
P	**p_2=0.395**			
DM	**7**	**28.0**	**7**	**28.0**
P	**p_2=1.000**			
Unknown	**2**	**8.0**	**4**	**16.0**
P	**$^{FE}p_2$=0.667**			
Glomerulonephritis	**0**	**0.0**	**0**	**0.0**
P	**-**			
Pregnancy complication	**1**	**4.0**	**1**	**4.0**

P	**p_2=1.000**			
ADPKD	**0**	**0.0**	**2**	**8.0**
P	**$^{FE}p_2$=0.490**			
Analgesic nephropathy	**1**	**4.0**	**0**	**0.0**
P	**p_2=1.000**			
Obstructive uropathy	**0**	**0.0**	**2**	**8.0**
P	**$^{FE}p_2$=0.417**			
SLE	**0**	**0.0**	**0**	**0.0**
P	**-**			
Chronic pyelonephritis	**0**	**0.0**	**0**	**0.0**

p: p value for Chi square test
^{FE}p: p value for Fisher Exact
p_2: p value for comparing between group A and group B

Hypertension and diabetes mellitus are the most common causes of CKD across all our groups. There was no significant difference in the demographic characteristics of CKD etiology between the two groups of group (group A and group B) **Table (4)**

Table (4): Comparison between hemoglobin rise in the two groups of group at the end of the study, group A was on low fixed dose ESAs and group B was on high fixed dose ESAs:

Hemoglobin increase Till 6th month	**Group II**	
	C (n=25)	**D (n=25)**
Min. – Max.	**-1.10 – 1.80**	**-0.80 – 4.30**
Median (IQR)	**1.10(0.7 – 1.5)**	**1.90(1.1 – 2.4)**
p	***p=0.004****	

p: p value for Mann Whitney test for comparing between group IIC and group IID
***: Statistically significant at $p \leq 0.05$**

There was a significant difference in hemoglobin rise in favor of the high dose ESAs group. **Table (4)**

Figure (1): Follow up of hemoglobin levels in group during the study.

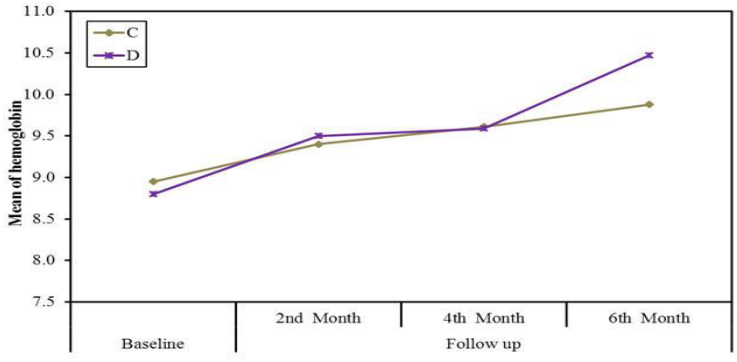

Table 5, Correlation between hemoglobin rise at the end of the study and Urea reduction ratio (URR) in group:

		Hemoglobin rise after 6 months
URR	r_s	0.536
	P	0.006

r_s: Spearman coefficient
***: Statistically significant at p ≤ 0.05**

Higher dialysis adequacy had a positive effect on higher hemoglobin levels at the end of the study. **Table (5)**

Table (6): Correlation between hemoglobin rise at the end of the study and baseline iPTH level

		Hemoglobin till 6th month	
		Group A	**Group B**
PTH	r_s	**-0.156**	**-0.117**
	p	**0.456**	**0.576**

r_s: Spearman coefficient
***: Statistically significant at p ≤ 0.05**

There was non significant weak negative correlation between baseline PTH level and hemoglobin levels at the end of the study. **Table (6)**

5. DISCUSSION:

We divided group into two groups, group A and group B. The baseline mean hemoglobin of group A was 8.95 (± 0.98) while the baseline mean hemoglobin of group B was 8.80 (± 1.16). The dose of ESAs in ESKD patients in Egypt is not only a matter of achieving higher hemoglobin a level, it also presents a form of an economic challenge. Egypt is a Lower-middle-income economy according to the world bank with a GDP (PPP) per capita of 13,366$ according to the international monetary fund (ranked 94th worldwide). The cheapest ESAs in the Egyptian market costs about 120 EGP (about 7.5$), so most Egyptian ESKD patients rely on their monthly ESAs supply from the government.

This monthly supply is usually about 4 to 6 Epoetin alfa (4000 IU) ampoules which makes most of the Egyptian ESKD population nearly on a low and fixed dose. Being on a low dose of ESAs isn't always bad if it keeps hemoglobin level within acceptable levels and it also might help decrease the incidence of some of the adverse effects of using ESAs. Group A were put on a fixed dose of 4000 IU Epoetin alfa once weekly and group B were put on a fixed dose of 4000 IU Epoetin alfa three times weekly.

We assessed the difference in response in hemoglobin level after 6 months. We found a significant difference in hemoglobin response of the two groups in favor of group B (P = 0.004).

Our results had a similar pattern to the initial 3 months results of a year long multicenter randomized clinical trial comparing low versus high dose ESA doses in anemic hemodialysis patients by Saglimbene and colleagues[8].

However, researchers in that study didn't have a fixed doses strategy, they also started with a higher baseline mean hemoglobin than ours in both the low and high doses group (both were 11.0 *(±1.0)*). Consequently, hemoglobin rise after the initial 3 months began to exceed the acceptable levels and the researchers had to decrease the dose, so treatment doses started to

converge after the initial 3 months. At the study end, complete convergence of hemoglobin levels occurred.

Higher hemoglobin targets are thought to be associated with hypertension, increased risk of cardiovascular events and vascular access thrombosis [9].

In our study, we found no significant difference in pre-dialysis session blood pressure between both groups A and B. Our 6th month mean of blood pressure in group A was 132.6 (± 23.4) and in group B was 137.2 (± 21.2). There was also no significant difference in vascular access thrombosis in the 2 groups (two cases in group A and three cases in group B). Fortunately, we witnessed no major cardiovascular events in our study group.

Our good fortune with cardiovascular events may be (at least in part) because we started with a low mean hemoglobin level in both groups. Another contributing factor might be the relative short period of our study (6 months).

However, there is a growing suspicion that the adverse effects are not only related to the higher hemoglobin levels but also the higher ESAs doses in itself irrespective of hemoglobin levels may play a role in the adverse effects [10]. However, this suspicion may be refuted by the fact that the need for higher ESAs doses usually arises in cases with comorbidities that in turn may cause ESAs hypo-responsiveness, so this association between higher ESAs doses and adverse effects may not be the direct cause and effect relationship some believe.

There is an ongoing clinical trial that will be completed in 2022 that will test the difference in effect between low and high doses ESAs on cardiovascular events independent of hemoglobin levels through monitoring the progression of carotid plaques by radiological means (MRI) [11].

In light of these uncertainties, we concluded that individualization of the ESAs dose is the safest strategy. Dosing process should consider baseline hemoglobin, targeted hemoglobin, patients' response, comorbidities and general condition.

Another finding observed in our study was the positive correlation between better dialysis adequacy and higher hemoglobin levels (r_s = 0.536). The same finding was observed in the study by Gaweda and colleagues, [12] . This correlation may be due to the role of uremic toxins in inhibiting erythropoiesis.

Hyperparathyroidism is associated with decreased erythropoiesis Drueke and Eckardt [13] , this may be due to the increased bone marrow fibrosis and the hormonal effect on erythroid precursors. This hormonal effect is explained by the fact that erythropoietin cells express calcitriol receptors inducing proliferation and maturation of erythroid progenitor cells, so calcitriol deficiency (which is a cause of hyperparathyroidism) may also has an inhibitory effect on erythropoiesis[14].

In our study, iPTH level for group A 191.28 (± 68.68), in group B 166.0 (± 81.18). In our study, groups showed a weak negative correlation between iPTH level and hemoglobin level (r_s in groups = 0.272).

Studies by Adhikary and colleagues [14] and Gaweda and colleagues [12] showed the same weak negative correlation pattern between iPTH levels and hemoglobin levels. However, studies by Chutia and colleagues, [15] and Sliem and colleagues, [16] found a strong negative correlation between them.

The weak negative correlation between iPTH levels and hemoglobin levels in our study may be due to the corrective measure for hyperparathyroidism like vitamin D and calcium our patients (sometimes excessively) receive.

Limitations of our study are relative short period of the study and the small number of included patients. We recommend a longer period, multicenter and nationwide study with more emphasis on possible cardiovascular adverse effects to reach a more solid consensus on the suitable ESAs dose in Egyptian CKD population.

6. CONCLUSION:

We concluded that low dose ESAs is less effective in correction of anemia in dialysis patients than high dose ESAs. After 6 months, we found a significant difference in hemoglobin level raising between the two sets of patients in favor of the patients who received the high dose. We also found no significant difference in adverse effects between the two groups. However, due to various reports on the adverse effects of ESAs in addition to the economic considerations, we concluded that the better option will be individualization of the dose according to the condition of the patients. We also found that dialysis adequacy to be linked to higher hemoglobin levels while iPTH had a weak relation to hemoglobin levels.

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