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Biochemical Changes in Relation to Blood Hemoglobin of Anemic Heamodialysis Patients Treated with Mircera at AL- Hussein Dialysis Center in Thi-Qar Province / Iraq

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Abstract
Background : Anemia is a reduction in the number of RBC count and resulting mainly from reduced erythropoietin production due to the damage or loss of kidneys function in chronic renal failure (Renal anemia) and is a common complications in hemodialysis patients.
The objectives: This study design to evaluate the changes in some biochemical parameters and the relation with blood hemoglobin, for post-heamodialysis patients treated with stable dosage of Mircera (Methoxy polyethylene glycol - epoetin beta 75 µg/0.3 ml, Germany).
Patients and method: Blood of 95 patients were collected from AL- hussien dialysis center in Thi-Qar province / Iraq within three months period, number of dialysis session was two time per week for two hours each session. After heamodialysis session, patients treated with stable dosage of Mircera (0.6 µg) for every kilogram of body weight once every 2 weeks . The data and biochemical finding of their blood sample collected after heamodialysis session.
Results: A ninety fife HD patients included 65 (68.4%) were male and 30 (31.6%) were female, aged between 19 to 65 years, their total body weight was 59.34 ± 1.33 Kg and their blood analysis are normal glycemia 5.4 ± 0.51 mmol/l , normal natraemia 137± 0.77 mmol/l, but hyperkalamia (6.1 ± 0.9 mmol/l) , hyperuraemia (21.78± 4.13 mg/dl) , hypercreatinaemia (2.2 ± 0.98 mg/dl) , and the mean HB value was (8.38 ± 1.18 g/dl). The results of response to Mircera show only one patient (1.05 %) had mean HB values (12.0 g/dL) within the target range recommended by KDOQI guideline. Seventy patients (73.69 %) had mean HB value between 8.0 to 10.9 g/dL, twenty four patients (25.26 %) had mean HB values between 5 - 7.9 g/dL and there are no one (0.0 %) had exceed the recommended range (>12 g/dL). Anemia degree positively related with hyperuraemia and hypercreatinaemia .
Conclusions: There are Hyporesponsiveness to mircera (75µg/0.3 ml) therapy in hemodialysis patients associated with reducing dialysis efficiency slightly for potassium, urea and creatinine and that positively related with anemia degree .
Keywords: Anemia , Mircera , Blood Urea, Blood Creatinine and Heamodialysis patients.

Introduction

Chronic kidney disease (CKD) is a global health problem, widely prevalent, and still increasing. ESKD patients requires cost-prohibitive kidney replacement therapy[1]. A hemodialysis machine has a special filter called a dialyzer, or artificial kidney, to clean blood from waste product such as creatinine and urea also mentaince the disturbances in water, electrolyte and acid– base balance, when kidneys are in a stage of renal failure. [2]

The procedure of haemodialysis is performed two to three times in a week and the time of dialysis is from two to four hours. The time of dialysis depends on various factors, including kidney function, amount of waste in body, level of salts and body weight. Mortality rate with haemodialysis remains high (approximately eighteen to twenty percent per year) [3].

Anemia is a common complication of CKD that develops early in the course of the disease increasing its frequency with the decline of renal function as in the figure 1 if kidney cannot make enough of EPO tells the body cannot makes red blood cells and without enough EPO, red blood cell count will drop and anemia will develop [4-6]. The incidence of anemia is less than 2 % in CKD stages 1 and 2, about 5% in CKD stage 3, in CKD stage 4 its 44% and more than 70% in the end-stage renal disease (ESRD) [7].

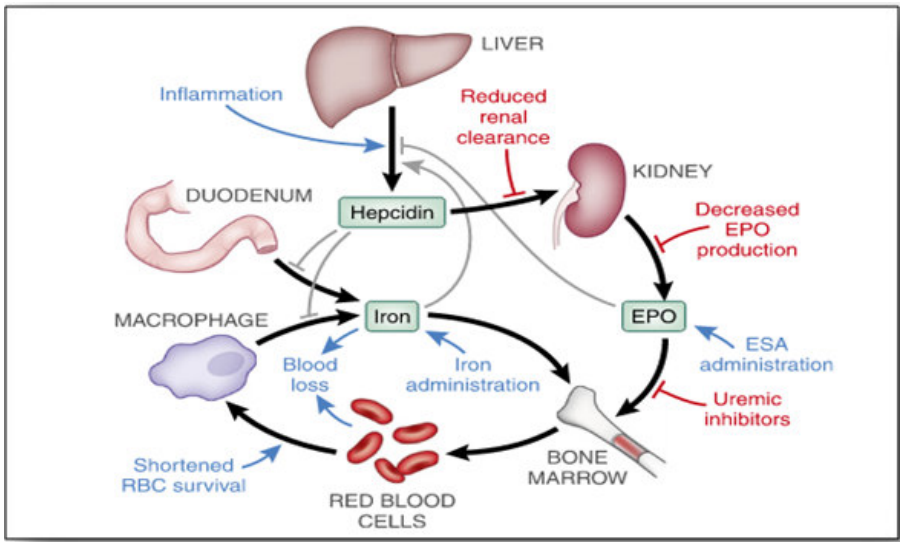

Figure 1: The mechanisms underlying anemia of CKD. Black and gray arrows represent normal physiology (black for iron and hormonal fluxes, gray for regulatory processes). Colored arrows represent the additional effects of CKD (blue for activation, red for inhibition). RBC, red blood cell [4-6].

RBCs carry oxygen from lungs to all parts of the body, giving the energy need for daily activities and diagnosed by measuring hemoglobin (HB) level (g/dL). Normal limits vary in the general population [8]. According to the World Health Organization, normal HB is defined as 13 g/dL in men and 12 g/dL in women [9]. The definition of anemia in general is a hemoglobin value < 13 g/dL for males and < 12 g/dL for non-pregnant women [10]. In anemia there are a poor capacity of blood to carry oxygen, because of red blood cells are in short supply.

Anaemia should be treated in order to achieve the benefits of increased exercise capacity and quality of life[11,12].The correction of anemia in CKD patients needs pharmaceutical intervention with erythropoiesis stimulating agents (ESAs) act like the natural hormone EPO, which helps the body to make red blood cells, Whenever possible, blood transfusions should be avoided in order to minimize the risk of human leukocyte antigen (HLA) sensitization and the probability to be infected with C virus [13]. Iron supplementation, as adjuvant therapy, should be administrated to prevent iron deficiency and minimize the dose of ESA needed to achieve the target range of Hb levels 11-12 g/dl [14,15]. Basically, there are three generations of ESAs: epoetin alfa (first generation), darb-epoetin (second generation) and methoxy polyethylene glycol-epoetin beta. Successive generations acquired longer half-lives as in the table 1[12].

Table 1 : Generations of erythropoiesis- stimulating agents (ESAs) and their half-lives value in hours[12] .

Erythropoietin-stimulating agents	Half-lives in hours	
	Intravenous route	Subcutaneous route
Epoetin	6.8	19.4
Darbepoetin	25.3	48.8
Methoxy polyethylene glycol-epoetin	134	139

Methoxy polyethylene glycol-epoetin beta (Mircera) is the only ESA that is generated by chemical modification of glycosylated erythropoietin through the integration of one specific, long, linear chain of polyethylene glycol. This ESA induces continuous erythropoietin receptor activation and has a long half-life (approximately 130 hours), injection is significantly less painful [16]. The first evidence of a response to ESAs is an increase in, haemoglobin usually within 2 to 6 weeks [12].

This study design to evaluate variability of Hemoglobin in relation to blood urea and creatinine of post heamodialysis patients and asses the response for the treating with ESAs by comparing observed practice to the Kidney Disease Outcomes Quality Initiative (KDOQI) guideline recommendations and show if the treating with Mircera effect on the response to heamodialysis therapy.

Patients and methodology

This study was conducted at AL- hussien dialysis center in Thi-Qar province / Iraq, predominantly 95 patient with chronic kidney disease in end stage were collected within a three months period. The mean duration of heamodialysis sessions was 3 hours per day and 2 time per week using polysulfone high-flux dialyzer 17 L, its membrane area 1,7 m^2 .

After heamodialysis session, patients treated with stable dosage of Mircera (methoxy polyethylene glycol-epoetin beta 75 µg/0.3 ml, Mannheim, Germany) . Starting dose of Mircera is 0.6 µg for every kilogram of body weight once every 2 weeks. The data and biochemical finding of their blood sample collected after heamodialysis session were performed by approved methods.

Statistical analysis

Descriptive statistics and frequency distributions were computed for all the variables and Chi-square test was used for categorical data by using SPSS version 19.00.

Results

In table 2 we can show data descriptive of 95 HD patients , of these 95 patients 65 (68.4%) were male and 30 (31.6%) were female, aged between 19 to 65 years, their total body weight was 59.34 ± 1.33 Kg and biochemical finding are normal blood sugar 5.4 ± 0.51 mmol/l, and normal natraemia (137 ± 0.77 mmol/l) , hyperkalamia (6.1± 0.9 mmol/l), hyperuraemia but with low risk level (21.78 ± 4.13 mg/dl) , hypercreatinaemia (2.2 ± 0.98 mg/dl) and the mean HB value was 8.38 ±1.18 g/dl .

Table 2: Data descriptive of 95 HD patients.

Patients data	Number
Gender (M/F)	65 (68.4%) / 30 (31.6%)
Age	19-65 year
TBW	59.34 ± 1.33 Kg
Blood sugar	5.4 ± 0.51 mmol/l (3.6-6.1 mmo/l)*
Blood Sodium	137 ± 0.77 mmol/l (135-145 mmol/l)*
Blood Potassium	6.1 ± 0.9 mmol/l (3.5- 5 mmol/l)*
Blood Urea	21.78 ± 4.13 mg/dl (5-20 mg/dl)*
Blood creatinine	2.2 ± 0.98 mg/dl (0.6 to 1.2 mg/dl)*
HB	8.38 ± 1.18 g/dl

*Normal value of blood sugar, Sodium, Potassium, Urea and creatinine[17-19].

The results of the variability of HB level and the treating anemia program with Mircera after dialysis session of CKD patients illustrated in table 3 and figure 2, show only one patient (1.05 %) had mean HB values between 11.0 and 12.0 g/dL the target range recommended by KDOQI guideline. Seventy patients (73.69 %) had mean HB value between 8.0 to 10.9 g/dL. Twenty four patients (25.26 %) had mean HB values between 5 - 7.9 g/dL and there is no one patient (0.0 %) had exceed the recommended range (>12 g/dL).

Table 3 : The distribution of patients based on HB values to target haemoglobin levels (11–12 g/dl) with stable dosage of MIRCERA (methoxy polyethylene glycol-epoetin beta 75 µg/0.3 ml) 0.6 micrograms for every kilogram of body weight once every 2 weeks around three months of treatment .

Patients group according target hemoglobin levels (11–12 g/dl)	**Patients number**	**Percentage %**
Greater than 12 g/dL	0.0	0.0
Between 11.0 and 12.0 g/dL	1	1.05
Between 8.0 to 10.9 g/dL	70	73.69
Between 5 - 7.9 g/dL	24	25.26
Total	95	100.00

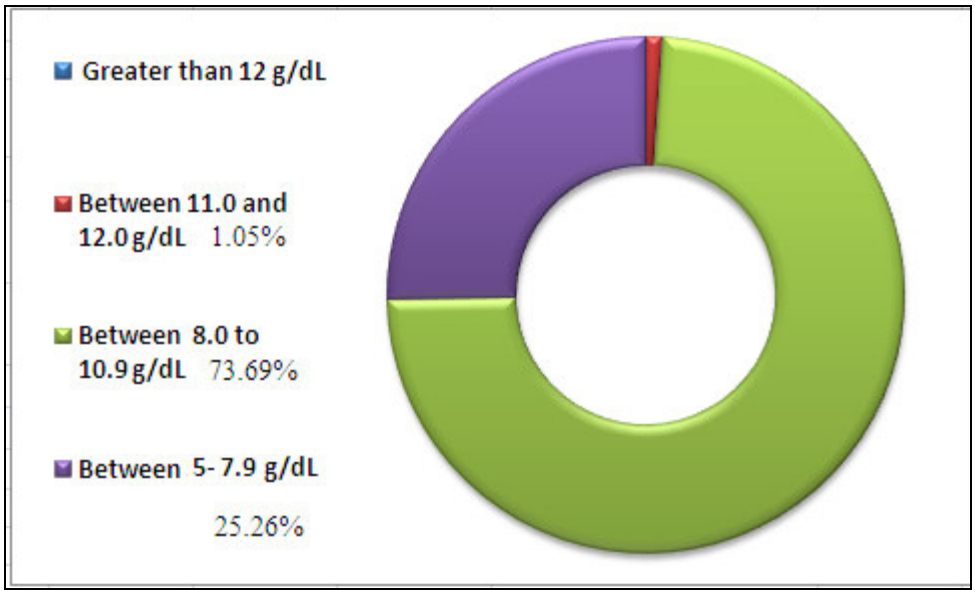

Figure 2: The distribution of patients based on HB values to target haemoglobin levels (11–12 g/dl) with stable dosage of MIRCERA (methoxy polyethylene glycol-epoetin beta 75 µg/0.3 ml) 0.6 micrograms for every kilogram of body weight once every 2 weeks around three months of treatment .

Figure 3, show high positive relation between hyperuraemia and hypercreatinaemia in post-heamodialysis patients. Figure 4 and figure 5 explain the correlation between the decreasing of blood hemoglobin and increasing the incident of hyperuraemia and hypercreatinaemia respectively.

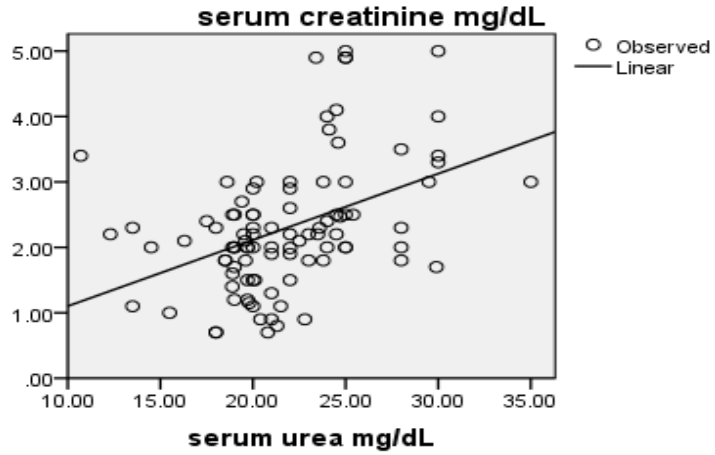

Figure 3: The correlation between blood creatinine and blood urea.

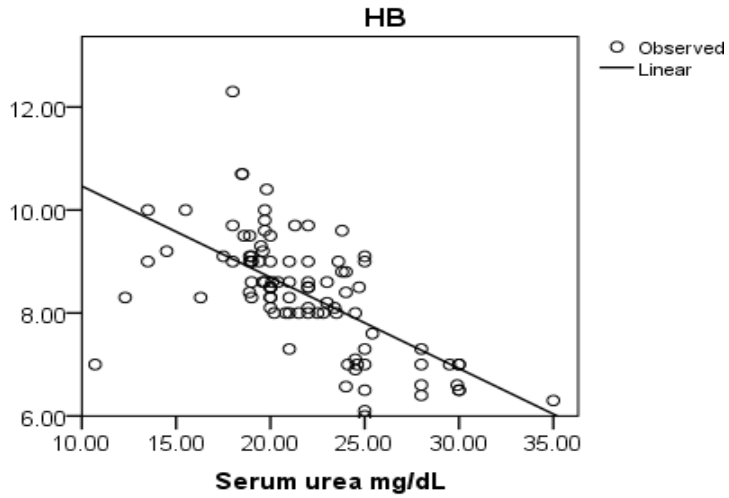

Figure 4 : The correlation between blood hemoglobin and blood urea.

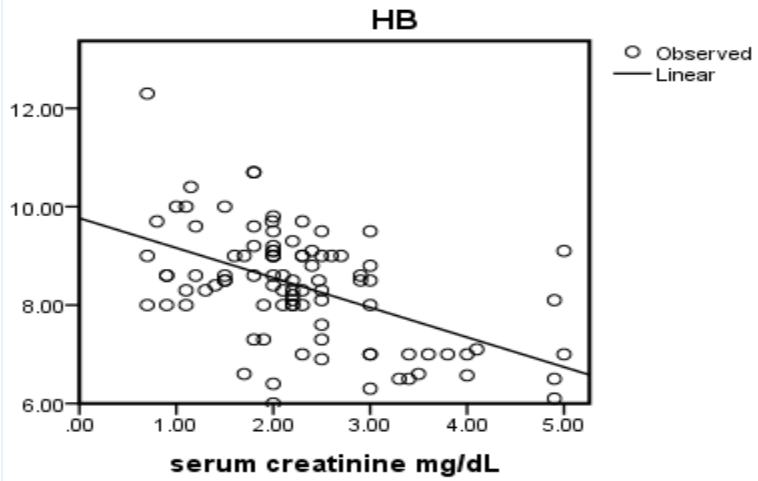

Figure 5: The correlation between blood hemoglobin and blood creatinine

Discussion

Dialysis is a process of separating the soluble crystalloids from the colloid is a mixture by means of a dialyser. Dialysis is based on the principle of diffusion equilibrium. In general dialyzing fluid (Dialysate) contains Na^+, K^+ and HCO^{3-} in a higher concentration than normal plasma (urea, urates, creatinine, phosphate and sulphate are absent). If the plasma K^+ of patient is above normal, K^+ diffuses out of the blood across the cellophane tubing and in to the dialyzing fluid. Similarly, waste products and excess of the substances also diffuse in to the dialyzing fluid and thus are removed from the body[20].

In theses cases the hyperkalemia is may be thought to result from the failure to follow dietary potassium restrictions and ingestion of medications that contain potassium, or from an endogenous release of potassium, as in case of trauma or infection [21].

On other hand, inadequate dialysis due to noncompliance or vascular access problems, medications such as ACEIs, [K] sparing diuretics, non-selective beta blockers, NSAIDs, and un fractionate heparin use [22]. The prevalence of hyperkalemia in any given month of HD patients was reported to be about 8.7-10% [23]. This point is very important to have attention because of some study found that , the mortality related to the hyperkalemia has been shown to be about 3.1/1,000 patient-years and mainly related to cardiac rhythm disturbances. So, it is frequently called "a silent and a potential life threatening killer" among patients with ESRD under maintenance hemodialysis [83]. Potassium is easily removed by dialysis, but when it builds up in the blood between treatments, it can cause muscle weakness and make the heart stop beating. Certain fruits, vegetables, dairy products and other foods that are high in potassium will need to be restricted from diet[25].

Nearly all patients had urea and creatinine levels above the therapeutic range, an elevated creatinine level before dialysis means remaining a long time without dialysis, factors like age, sex and physical status of person also effect serum creatinine level [26]. Generally, in patients with end stage renal functions GFR < 15 mL/minute/1.73 m^2 , pre- dialysis serum potassium, urea and creatinine level was significantly higher 60% than normal range and after regulated dialysis sessions there are a clear reductions in blood sodium, potassium, urea and creatinine about 26-40% [27-29].

Hemoglobin level was low in HD patients (8.38 ± 1.18 g/dl) and the results above in table (3) give us an idea about the blood haemoglobin changes and correction with Mircera, HD patients respond adequately to ESAs is only 1.05 % and the majority of HD patients develops resistance to this therapy had mean Hgb values less than target level , that may be explained as a results for several factors like increased destruction of red blood cells due to chemical effects of uremic toxins; platelet dysfunction provoking blood loss, usually due to occult bleeding; blood loss due to clotting inside hemodialyzers and sets during HD sessions; hemolysis associated with contamination of dialysate water; and water-soluble losses of folate and vitamin12 through hemodialyzer membranes, affecting red blood cell production , during dialysis HB level of patients decreased to dangerous level, which is responsible for anemia [30-32]. Hypoxia stimulates the renin-angiotensin-aldosterone system and contributes to renal vasoconstriction [33].

The resistance to the effect of Mircera may be caused by the variability to the presence of concurrent medical problems between patients [34]. Additional reasons include acute or chronic comorbidities[35]; alteration in iron stores[36]; infection or inflammation [37,38] blood loss or transfusion [39]; dialysis treatment features such as dialysis adequacy [40]or water quality [41]; stage of CKD and residual renal function [42]; level of parathyroid hormone [43]; vitamin and mineral status such as vitamin D, B_{12}, or folate deficiencies[44]; and seasonal effects [45]. Decreased iron stores or decreased availability of iron are the most common reasons for

resistance to the effect of these agents. Dialysis patients commonly suffer iron loss from gastrointestinal bleeding, blood drawing, and/or, most important with hemodialysis, the dialysis treatment itself. Hemodialysis patients lose an average of 1 to 2 g of iron per year [46]. Thus, iron deficiency will tend to develop in virtually all dialysis patients unless supplemental iron therapy is given [42] In stage 5 of CKD characterized by a very high activated inflammatory status. Thus, CKD itself is a central cause of hyporesponsiveness to ESA, and because it is irreversible, it cannot be significantly modified [48].

ESAs resistance is associated with poor outcome, increasing the risk of mortality [49-51]. However, varies considerably between countries, reflecting variability in practice patterns [52] According to the data from an observational time and motion study, and that not accepted with another publisher studies , it is not the sole cause. Indeed, according to kidney Disease Outcomes Quality Initiative (NKF KDOQI) guidelines anemia of CKD is resistant to ESAs in approximately 10%-20% of patients which found response to the treatment [14]. Strategies will prove effective for treating anemia of CKD in humans remain unknown, blocking hepcidin and/or increasing ferroportin activity, these agents could improve dietary iron absorption and iron mobilization from the patients'own body stores, thereby minimizing the need for super physiologic doses of intravenous iron and ESAs with their potential adverse effects[53,54].

The statistical findings in figures 3,4, and 5 from the correlation tests between urea, creatinine and heamoglobin, show a high relation between hyperuraemia , hypercreatinaemia, and anemia on hemodialysis (HD) patients ,that prove the increasing of anemia stall as kidney function decreased as a results of the glomerular lesions , the glomerular filtration dysfunction, and also inevitably damage the juxtaglomerular cells, erythropoietin cytokine secretion reduce the impact to the bone marrow red blood cell production[5]. Of course, serum creatinine, blood urea nitrogen increased, and some other toxic substances in the blood also inhibit the bone marrow itself, but also affect the metabolism of iron and folic acid generate the hemoglobin of the raw materials[6]. Particularly in end stage kidney disease hepcidin levels have been found to be highly elevated, presumably due to reduced renal clearance and induction by inflammation, leading to iron restricted erythropoiesis, also circulating uremic-induced inhibitors of erythropoiesis, shortened red blood cell lifespan as in the figure 1 [5,6]. treatment of renal anemia with recombinant human erythropoietin in chronic hemodialysis patients has been reported to lead to increased appetite, [55] therapy for anemia in chronic renal failure patients could have unfavorable renal effects since reversal of anemia can raise blood pressure and accelerate experimental glomerular injury , the findings indicate that EPO treatment reduces dialysis efficiency slightly for a number of substances, but in the metabolically stable patient there are no impressive dietary changes. Problems can be overcome by appropriate changes of dialysis regimen and medication[56].

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