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Erythropoietin and Anaemia in Patients with Chronic Renal Failure

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Abstract
Hyporegenerative anaemia is common complication of chronic renal failure CRF and responsible for fatigue and reduced general health condition among uremic patient. The main causes of anemia among patients with chronic renal failure are deficient production of erythropoietin (EPO), iron deficiency, and chronic disease with endogenous EPO resistance.
This study confirmed on patients with chronic renal failure in Merjan Teaching Hospital and highlighted on the relationship between anaemia and erythropoiten level. The estimation of hemoglobin among patients with CRF revealed that 55% of patients suffered from severe anaemia and 45%suffered from moderate anaemia Erythropoiten level estimated by ELISA technique and mean and standard deviation of erythropoietin level among patients and control groups were12.2 uU/ml ± 2.6, 7.3uU/ml± 1.8 respectively and comparism mean of erythropoietin between patients and control group was indicated that there is significant difference between two groups at p value< 0.05
By study the correlation between hemoglobin and erythropoietin revealed that there is inverses relation ship between hemoglobin and erythropoietin , we concluded from this study although the level of erythropoietin increase in patients with CRF but the level of erythropoietin are not enough foe correction of anaemia and patient may required for exogenous source for erythropoietin with iron supplement in management of anaemia
Keywords: erythropoiten Hyporegenerative anaemia

1. Introduction

The definition of chronic kidney disease has been simplified over the last 5 years. It is now defined as the presence of kidney damage for a period greater than 3 months. An estimated or measured glomerular filtration rate of less than 60 mL/min/1.73 m^2 is considered abnormal for all adults. A rate of more than 60 mL/min/1.73 m^2 is considered abnormal if it is accompanied by abnormalities of urine sediment or abnormal results of imaging tests, or if the patient has had a kidney biopsy with documented abnormalities (Andrew *et al.* 2010) . Anemia is prevalent among patients with an estimated glomerularfiltration rate less than 60 mL/min/1.73 m^2 (De oilva R *et al.* 2006) **.** Anemia is associated with adverse outcomes in patients with chronic kidney disease, including hospital admission ,cardiovascular disease and mortality (Culleton2006&Jurkovitz*etal.2003).* Erythropoietin (EPO) is a 30.4 kD glycoprotein and class I cytokine consisting of 165 amino acids .EPO has four acidic oligosaccharide side chains (3 N-linked and 1 O-linked) and contains up to 14 sialic acid residues. Its carbohydrate portion contributes to 40% of its molecular weight (Mocini *et al.* 2007) **.**The N-linked polysaccharide side chains appear to be important for the biosynthesis and secretion of EPO ,enhance its stability in blood, and limit hepatic clearance ,thus facilitating the systemic transit of EPO from kidney to bone marrow (Boissel *et al.*1993) **.**The variable nature of the sialic acid content gives rise to EPO isoforms with differences in charge. As the number of sialic acid groups on the carbohydrate portion of EPO increase, so does its serum half-life ,whereas receptor-binding capacity decreases (Catlin *etal.*2002& Elliott *etal* .2002& Rush *et al*1995& Rush et al1993&. Middleton et al1993) .
Clearance, however, appears to have a stronger influence on in vivo activity than receptor-binding affinity. Each EPO molecule has two EPO receptor (EPOR)binding sites. There are two affinities of the EPOR for EPO in solution: one of high and one of low affinity (needs 1,000 times the concentration of EPO for activation (Weidemann *et al.***2009**).
The principal physiological function of EPO is red blood cell production, which results from a tightly controlled proliferation and differentiation pathway (Salahudeen *et al.***2008).** Early hematopoietic progenitor cells differentiate into burst forming unit-erythroid cells (BFU-Es).
Continuous stimulation with EPO triggers the differentiation of CFU-Es into erythroblasts, which lose their nuclei to form reticulocytes. After a few days, reticulocytes lose reticulin and become erythrocytes (red blood cells). Reticulocytes and erythrocytes stop expressing EPOR and decrease being responsive to EPO (Silva *et al***1999).**
Although erythropoietin deficiency is a well known cause of anemia in this population, the guidelines recommend that other potential causes of anemia should be sought(eg., iron deficiency) and treated accordingly The oral form of iron is the preferred first-line therapy for patients with chronic kidney disease Patients who

donot achieve serum ferritin or transferrin saturation targets or both while taking the oral form of iron or who do not tolerate the oral form should receive the intravenous form of iron to decrease complication of anaemia(Drueke *et al.* 2006& Singh *et al.* 2006& Phrommintikul *et al.* 2007 Based on this evidence, a target hemoglobin level of 110 g/L is recommended for patients with chronic kidney disease (acceptable range 100–120 g/L)(. Hemmelgarn *et al.* 2010) **.**

There are a number of common pathways through which EPO exerts its erythropoietic effects that also appear to confer tissue protection(Silva *et al***1999).** EPO "classically"binds to two EPORs, which become joined as a homodimer and change. This activates JAK2, which is bound to the common beta subunit of the EPOR(Percy *et al.* 2008& Li F *et al.* 2004). and leads to phosphorylation of tyrosine residues of the EPOR, which activates a number signaling pathways that promote cell survival and antiapoptotic effects through inhibition and inactivation of caspases, and prevention of cytochrome C release(Chatterjee *et al.* 2007) .These effects not only enhance the erythropoietic properties of EPO but appear to be important in the protection of other cell types and may contribute to the renal protective effects from apoptosis and promot survival of renal tissue (Joyeux *et al.* 2005& Westenfelder *et al.* 1999) .

One line for management of anaemia is the use of erythropoiesis-stimulating agents for the treatment of anemia (Medicare and Medicaid 2010) . and use for management of anaemia in chronic renal disease (McGowan *et al.* 2008) .The use of erythropoietin as treatment should use with precaution and monitoring in patients with chronic kidney disease may associated with potential adverse outcomes, including increased blood pressure and thrombotic complications. They should be prescribed by a specialist with experience in prescribing these agents beside Iron therapy is an important component of anemia management(Bagshaw *et al.* 2008& Ostermann *et al.* 2007& Song *et al.* 2009& Endre *et al.* 2010) .

2. Materials And Methods

Selection groups ;Group1: patients with chronic renal failure attended Merjan teaching hospital

Group 2: Healthy persons act as control groups .Hemoglobin level was estimated for patients with chronic renal failure and diagnosis of anaemia were established according to WHO criteria for diagnosis of anaemia(WHO2008)**.** And this classification are representing in table no.1

Table 1. **Hemoglobin thresholds for diagnosis of anaemia.**

WHO's Hemoglobin thresholds used to define anemia (1 g/dL = 0.6206 mmol/L)		
Age or gender group	**Hb threshold (g/dl)**	**Hb threshold (mmol/l)**
Children (0.5–5.0 yrs)	11.0	6.8
Children (5–12 yrs)	11.5	7.1
Teens (12–15 yrs)	12.0	7.4
Women, non-pregnant (>15yrs)	12.0	7.4
Women, pregnant	11.0	6.8
Men (>15yrs)	13.0	8.1

Eythropoiten level estemsted by ELISA technique and the standared curve for estimation of erythropoiten were represented in figure no. 1

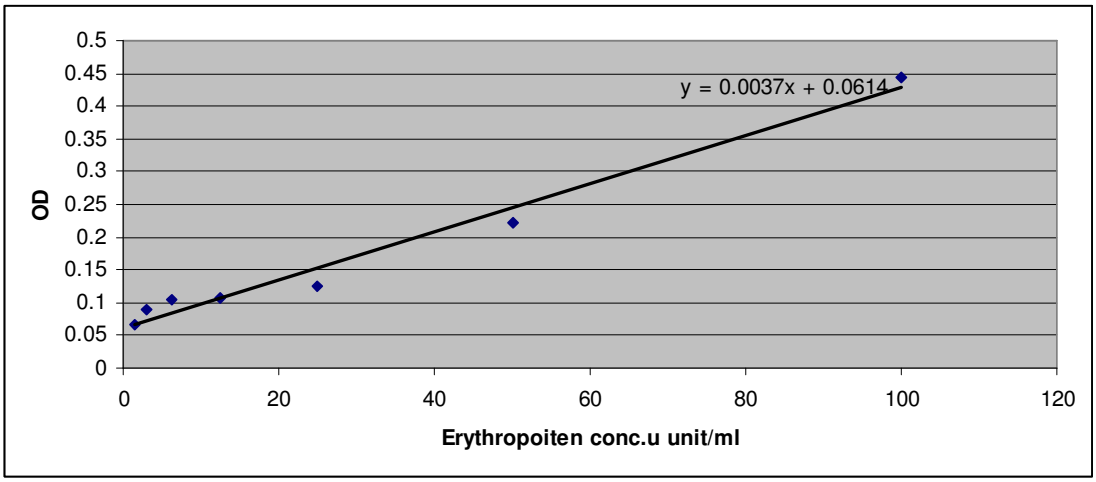

Figure 1. Standared curve of erythropoietin .

3.Results

Hemoglobin estimated for CRF patients and patients classified according to severity of anaemia , the patients with severe anaemia in which Hb<8 g/dl were 55% and patients with moderate anamia in which Hb between 8-11 gldl were45% and the result was representing in figure no .2

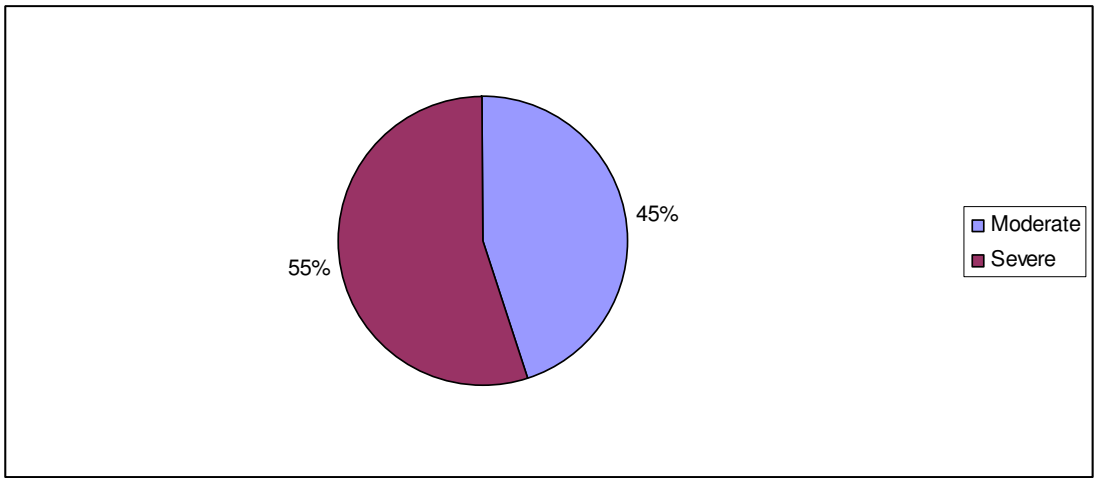

Figure 2. Severity of anaemia among patients with chronic renal failure.

Erythropoiten level estimated in sera of patients and control and the results were represented in figure no.3

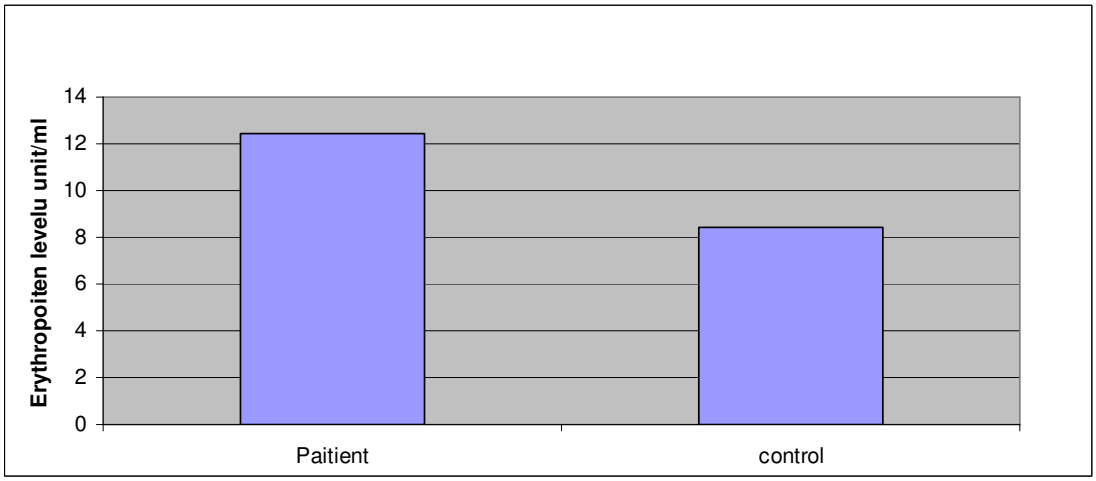

Figure 3. Erythropoiten level among CRF patients and control .

Analysis of data for the mean of erythropoiten level by students t-test was revealed that there are significant difference in estimated erythropoiten level between patients and control and the result was represented in table no. 2

Table .2 Erythropoiten mean difference between patients and control

	GROUPS	Mean ± SD u unit/ml	P value
Erythropoietin	**Patients CRF**	12.2 ± 2.6	**0.001***
	Healthy control	7.3± 1.8	

*p value<0.05 considered significant

Correlation between erythropoiten and PCV in patients with chronic renal failure were representing in figure no.4

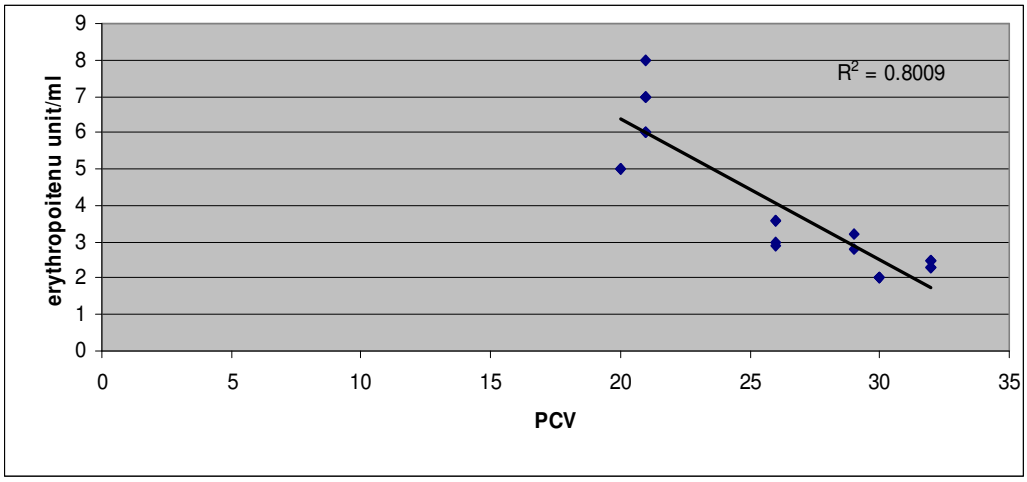

Figure 4. Correlation between erythropoitenlevel and PCV in CRF patients .

4.Discussion

The estimated hemoglobin in patients with CRD in this study revealed that about 55% of patients have severe anaemia and 45% of patients have moderate degree of anaemia according to WHO classification of anaemia .

Erythropoietin level estimation in patients with CRD and control groups and the mean and SD level of erythropoietin were 12.2uU/ml ± 2.6 in patients and7.3uUlml± 1.8 in control and by analysis of this data by student t test revealed that significant difference in mean between patients and control group at p value < 0.001 ,meaning that there is significant difference in erythropoiten level between patients and control The results of study indicated that the impact of anemia on patients with CKD is profound.

Anemia can develop in the early stages of kidney disease and get worse as renal disease progresses. Nearly all patients in end stage renal disease (the point where dialysis becomes necessary) have anemia (Zarychanski & Houston2008) .

In addition to the well known symptoms of fatigue, dizziness, and shortness of breath, anemia has been associated with more severe adverse outcomes, such as cardiovascular complications including left ventricular hypertrophy and congestive heart failure. Hypoxia caused by anemia stimulates the renin-angiotensin-aldosterone system and contributes to renal vasoconstriction. These factors further exacerbate proteinuria by increasing protein in the renal tubules in patients with renal failure(Al-Khoury *et al.* 2007) Other general complications associated with anemia include reduced cognitive function and mental acuity, impaired quality of life, and the need for blood transfusions(Scortegag M et *al.* 2005) **.**Meaning that anemia in chronic renal failure reacquired for a good management , the main stimulus for anamia is by secretion of erythropotien the primary stimulus for production of EPO is hypoxia ,a deficiency in tissue oxygen levels increases the activity of hypoxia-inducible factor 2a, which binds to hypoxia-responsive elements locate in the enhancer region of the *EPO* gene in order to activate transcription(Karine et *al.* 2011) **.**The analysis of data in this study revealed that the level of erythropoiten in patients with chronic renal failure are higher than in control but this elevation are insufficient to correct anaemia either due to insufficient secretion of erythropoietin level secretion from damaged kidney tissue or due to erythropoietin resistance this conclusion conferred by another study which indicated that the high EPO levels in patients with are inappropriately low for the degree of anemia (KDIGO 2012) .These data indicate that in CKD, there is a relative EPO deficiency as well as resistance of bone marrow to endogenous EPO. so although erythropoiten in patients EPO are higher than control but the increase in erythropoiten level according to anaemia degree are not enough for correct anaemia this results agree by studyof (Minutolo et *al.* 2012**).**

5. Conclusion

The patients with chronic renal failure develop severe form of anaemia with depletion of iron storage and inefficient erythropoietin that required for iron supplement and exogenous source of erythropoietin with follow up for patients

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