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Original Article

Hematological Changes in Patients of Chronic Renal Disease and Their Response to Treatment with Erythropoietin

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Abstract

Introduction: Anemia is a common manifestation of chronic kidney disease, especially when the glomerular filtration rate falls below 30 ml/min. For evaluation of anemia, it is important to exclude other causes of anemia such as iron and other hematinic deficiencies, chronic inflammation or the effect of drugs. After reversible causes of anemia are excluded, supplementary erythropoietin (EPO) can be considered when the patient's haemoglobin concentration falls below 11 g/dl.

Methodology: This prospective study was conducted at Nephrology unit of Holy Family Hospital Rawalpindi, from April- June 2014. Fifty diagnosed patients of chronic kidney disease presenting with anemia were included in the study. Their CBC was done on Sysmex KX21 to check their baseline parameters. About 4000 iu of EPO was administered subcutaneously to all patients for three weeks and CBC was done at the start of 4th week. Results were entered on SPSS version 17 for further analysis. P value of < 0.05 was taken as statistically significant.

Results: Total number of cases included during the study period was 50. Their age range was between 13-68 years with the mean age of45.1±1.64 SD. Among these 28 (56%) were males and 22 (44%) were females. Changes in hematological parameters in CKD patients were noted. Notable changes were seen only in Hemoglobin levels. Mean Hemoglobin before the start of treatment was 8.10gms/dl ± 0.107SD whereas after treatment mean hemoglobin increased to 8.93 ± 0.100 SD with highly significant p value of 0.000. MCH also showed a significant improvement with a mean MCH (before treatment) 31.43 ± 0.048 SD to mean MCH of 31.73+0.058 (after treatment) with a significant p value of 0.000. Changes in other hematological parameters were insignificant.

Conclusion: Among hematological parameters hemoglobin is the most commonly affected. Erythropoietin plays an effective role in increasing hemoglobin level in these patients.

Key words: Erythropoietin, Chronic kidney disease, Chronic renal failure, Hematological parameters, anemia.

Introduction

Diseases of the kidneys are among the most important causes of death and disability in many countries throughout the World.[1]Renal diseases are associated with a variety of hematological changes.[2] Anemia is the most common finding among these hematological manifestations and its severity increases with disease progression. Patients of chronic kidney disease (CKD) should be investigated for the cause of anemia if their hae-

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moglobin falls to 11 g/dL or less, or there are symptoms of anemia.[3]Anemia of chronic renal disease is usually normocytic and normochromic. There are many causes for anemia in these patients. These include iron deficiency, B12 or folate deficiency, functional deficiency of iron (due to impaired iron utilization for erythropoiesis), effects of dialysis, bleeding because of platelet function defect (effect of uremia on platelet, decreased synthesis of erythropoietin and decreased sensitization of erythroblasts to erythropoietin and the effect of drugs used for treatment. However among these the most common cause for anemia in CKD is decreased production of erythropoietin from the reduced mass of functioning renal tubular cells.

Erythropoietin (EPO) is Glycoprotein hormone produced by peritubular interstitial cells of kidney.[4] Under normal conditions circulating erythropoietin levels are usually low but in response to anemia or tissue hypoxia, these levels are increased many folds.[5] However in patients with CKD as a result of reduced functional mass of kidney this response is hampered. Thus this inadequate response of erythropoietin is generally insufficient to stimulate erythropoiesis and maintain hemoglobin level. Studies have shown that correction of anemia can limit the progression of disease and improve the quality of life in these patients. When anemia is found the patients should be evaluated for the cause of anemia. Reversible etiologies like nutritional deficiencies are corrected first and hemoglobin levels are reassessed before the diagnosis of secondary erythropoietin deficiency is made.

EPO can be administered intravenously (i/v) or subcutaneously (s/c). S/C administration provides a longer duration of action and is a preferred route. According to Clinical Protocol for the Use of Erythropoietin in Patients with Chronic Renal failure 2014, during the initial treatment with EPO therapy the haemoglobin should be checked on a monthly basis until a target haemoglobin range of 11-12 g/dl is achieved. The haemoglobin is then checked monthly or two monthly thereafter.[6] Patients on EPO are monitored every 2-4 weeks in induction phase and every 1-3 months in maintenance phase Current guidelines also suggest that EPO administration should be tailored to target hemoglobin between 11-12g/dl in patients with chronic renal disease. Iron stores should also be assessed following treatment with EPO as rapid erythropoiesis readily consumes iron stores so iron supplementation may be required for repletion of stores. Patients treated with EPO often require oral or intravenous iron supplements to maintain adequate iron stores during the initial or maintenance phase.[7]

The time taken for the effect of EPO will depend upon various factors such as degree of anemia, severity of kidney disease and presence of other adverse factors such as iron deficiency. Contraindications for EPO treatment include uncontrolled hypertension and thrombotic complications. However untreated anemia itself is associated with cardiovascular and renal complications and thus increased mortality. Therefore correcting anemia is considered an important factor in reducing mortality and morbidity in these patients. Treatable causes should be addressed first and if anemia still persists and no other cause is found patients should be put on EPO therapy. Treatment with EPO improves hemoglobin and reduces requirement for blood transfusion, thereby improving the quality of life in these patients.

Besides hemoglobin and red cell indices, white blood cells, platelets and coagulation factors may also be affected. However most of the authors have reported insignificant changes in total white cell count and platelet count in these patients.[8]

This study was conducted to look for hematological changes in chronic kidney disease and to see

the effect of EPO administration on hemoglobin and other hematological parameters.

Methodology

This prospective study was conducted at Nephrology unit of Holy Family Hospital Rawalpindi from April- June 2014. Fifty diagnosed patients of chronic kidney disease presenting with anemia were included in the study. After exclusion and treatment of other causes of anemia the patients were subjected to treatment with EPO. Their CBC was done on Sysmex KX21 to check their baseline parameters. About 4000 iu of EPO was administered subcutaneously to all patients. Erythropoietin (epokine) was given for three weeks and CBC was done at the start of 4th week. Dose of erythropoietin was increased if response to treatment was not obtained. All the patients were also given oral iron therapy with folic acid when they were found iron deficient. Patients with less than Hb <6gms/dl were given parenteral iron therapy. Results were entered on SPSS version 17 for further analysis. P value of < 0.05 was taken as statistically significant.

Results

Total number of cases included during the study period was 50. Their age range was between 13-68 years with the mean age of45.1±1.64SD. Among these 28 (56%) were males and 22 (44%) were females. Mean urea levels of these patients was 104 ± 4.629 and mean creatinine was 7.298 ± 0.291 SD. About 20 (40%) patients had associated Diabetes mellitus, whereas 48 (96%) patients were hypertensive. Hepatitis C Positivity was noted in 29 (58%) patients.

Mean Hemoglobin before the start of treatment was 8.10gms/dl ± 0.107SD whereas after treatment mean hemoglobin increased to 8.93 ± 0.100 SD. Table 1 shows mean values of hematological parameters before and after treatment. Assessment of these hematological parameters shows a significant improvement in hemoglobin concentration from 8.10gms/dl ± 0.107SD to 8.93 ± 0.100 SD with highly significant p value of 0.000. MCH also showed a significant improvement with a mean MCH (before treatment) 31.43 ± 0.048 SD to 31.73+0.058 with a significant p value of 0.000. Figure 1 shows changes in hemoglobin and red cell indices before and after treatment. Changes in other hematological parameters before and after treatment with erythropoietin are statistically insignificant.

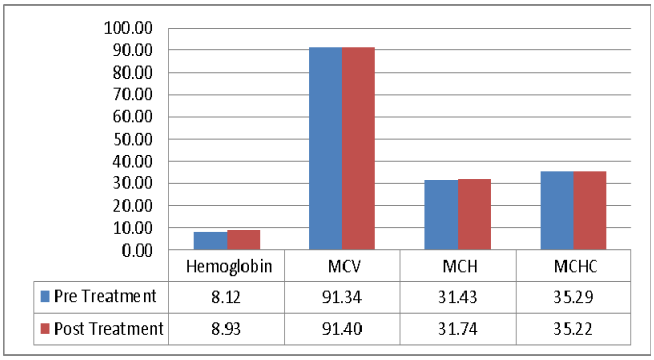

Figure 1: Comparison of Hemoglobin and Red cell indices before and after treatment

Table 1 shows mean and p values of all the hematological parameters before and after treatment with erythropoietin. Table 2 shows severity of anemia in both the groups. As shown in the table 21 (42%) of patients had hemoglobin less than 8 gms/dl before treatment with EPO whereas this percentage dropped to 8 % (4 patients). Moreover after treatment with EPO majority [46 (92%)] of patients had their hemoglobin level more than 8gms/dl. None of the patients post treatment had their hemoglobin less than 7gms/dl and none of pre treatment group had their hemoglobin more than10 gms/dl.

Table 1. Pre Treatment and Post Treatment Blood CP findings			
	Pre Treatment Range (Mean ± SD)	**Post Treatment Range (Mean ± SD)**	**P value**
Hemoglobin (gms/dl)	6.30-9.60 (8.1± 0.107)	7.10-10.20 (8.90 ± 0.100)	**<.05**
TLC ($X10^9$/l)	4.30-7.30 (5.32 ± 0.085)	4.10-5.90 (5.14 ± 0.063)	0.648
Platelet count ($X10^9$/l)	120-220 (169 ± 3.508)	126-225 (172.56 ± 3.06)	0.095
MCV (fl)	89-96.10 (91.33 + 0.12)	91.10-92.50 (91.39 ± 0.041)	0.455
MCH (pg)	30.50-32.20 (31.43 ± 0.048)	31.10- 32.60 (31.73 ± 0.068)	
MCHC (gms/dl)	34.20-37.10 (35.29 ± 0.14)	34.10-39.10 (35.22 ± 0.149)	0.719

Table 2. Anemia in Chronic Renal Failure Patients(N=50)		
Hemoglobin level (gms/dl)	Pre Treatment N (%)	Post Treatment N (%)
< 7	03 (6)	00 (0)
< 8	18(36)	04 (8)
< 9	22(44)	22 (44)
<10	07 (14)	20 (40)
> 10	00 (0)	04 (8)

Regarding platelet count only 6 patients had platelet count less than 140,000/µl. None of the patients had leukocytosis or leukopenia.

Discussion

Chronic kidney disease (CKD) is a progressive disease that results in significant morbidity and mortality. Anemia is an independent risk factor for the mortality in these patients. Various studies have been conducted to see hematological changes in CKD patients. Anemia is a common feature becomes more severe with disease progression. Studies of patients with CKD have shown that anemia was twice as prevalent in people with CKD as compared to general population and prevalence increased significantly with the stage of CKD.[9,10]

If left untreated, the anemia in these patients may be associated with other abnormalities like deterioration in cardiac function, decreased cognition and mental acuity, fatigue, and other signs and symptoms of anemia. All these complications particularly cardiac complications are one of the major causes for an increased risk of morbidity and mortality in these patients. So it is very important that these patients are monitored for the cause and severity of anemia and treated meticulously. Various therapeutic options available for the anemia of CKD include red blood cell transfusions, treatment of underlying cause and use of erythropoietin.

In this study we studied various hematological parameters and effect of erythropoietin on these parameters particularly hemoglobin. Majority of our patients were males and this is in agreement with available data, which suggested the male gender as a risk factor for CKD. We found quiet low hemoglobin levels in our patients (between 6.3-9.6 gms/dl). Similar values of hemoglobin concentration have been found in other studies (7.6 ± 2.6 and 8.83 ± 1.78)[2,10] and like our study anemia is mainly normochromic normocytic in these studies. They did not observe any significant change in other hematological parameters as compared to the control group, findings comparable to our study.

We found a significant improvement in hemoglobin of our patients in response to treatment with erythropoietin with a p value. The patients were followed for three weeks with promising results. Another study done in kidney centre Ka-

rachi also showed a significant improvement in hemoglobin and hematocrit with use of erythropoietin. In an 8 months follow-up of their 9 patients they observed significant improvement in hemoglobin within 3 months in their 8 cases. One of their patients required increase in dose of erythropoietin and responded well to the treatment thereafter. All their patients also showed a significant improvement in their general well being, without showing any effect on their blood pressure or any other complication.[11] Similar findings have been reported in a study done by Rysz J et al and they reported a significant improvement in both the general state of the patients and the life quality and thus decreased cardiovascular complications and the mortality of patients.[12]All of our patients were given subcutaneous erythropoietin. In various studies it has been reported that route of administration does affect the response and with subcutaneous administration lower doses of EPO may be required as compared to intravenous administration and it also has longer duration of action.[13]

In our study majority (94%) had moderate degree of anemia (hemoglobin between 7-10gm/d, these findings are comparable to another study done by Suresh M. and AO Shittu et al on hematological pattern of patients of chronic renal failure.[2,10]Arun S reported anemia in 98 out of 100 patients of CRF and 60% of their patients had moderate degree of anemia and almost 60% had normocytic normochromic anemia and they found a strong correlation of degree of anemia to the severity of disease.[14]However Talwar et al. observed microcytic hypochromic anemia in most of the patients of chronic renal failure.[15]

Regarding other hematological parameters about 6 patients (12%) in our study had their platelet count less than 140,000/µl. These findings are comparable to other studies.[2,10,14] In one of the study bleeding in CKD has been found to be associated with quantitative platelet reduction in 20 to 52% of their cases, though in majority of the cases this was due to platelet dysfunction (as a result of uremia).[16]

Majority of our patients were hypertensive (96%) and diabetics (40%) and almost all developed anemia in the due course of disease. It has been proposed that progression of chronic kidney disease can be delayed by good control of blood pressure, blood sugar and correction anemia with erythropoiesis stimulating agents. Patients should be followed monthly while treated with erythropoietin and should also be assessed for iron replacement therapy to obtain effective regimen of erythropoietin therapy.[17] However there is some debate with regards to target haemoglobin i.e. the haemoglobin concentration that should be aimed so as to get maximum benefits and to reduce potential adverse effects to a minimum.[18,19,20]There are no strict guidelines but various studies have proved that aiming and maintaining hemoglobin concentration at much higher levels may be associated with cardiovascular events (due to hypertension and thrombosis), Current guidelines for anemia management in chronic kidney disease recommend the maintenance of haemoglobin concentrations around 11gms/d.[21,22]

In one of the good review about optimizing use of erythropoietin in CRF (chronic renal failure) patients, recommendations are; start treatment with EPO (after excluding other treatable causes) at hematocrit of 30% or less, or on the basis of anemic symptoms; reach hematocrit around 35%; subcutaneous route is the most is suitable route for administration, detect and correct iron deficiency; closely monitor blood pressure and look for the reasons of hyporesponsiveness.[23]

Conclusion

Hematological parameters are commonly affected in CKD. Of all the parameters, red cell indices are

the ones commonly affected. Anemia in CKD is a known risk factor and untreated anemia leads to increased morbidity and mortality. Thus, management of anemia throughout the course of disease is essential. Erythropoietin is effective and gives promising results in increasing hemoglobin in these patients.

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