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International Journal of Current Research
Vol. 6, Issue, 04, pp.6361-6364, April, 2014

INTERNATIONAL JOURNAL OF CURRENT RESEARCH

ISSN: 0975-833X

RESEARCH ARTICLE

A STUDY OF ERYTHROPOIETIN LEVEL IN PATIENTS CONSIDERING THE SPECTRUM OF HEALTH AND DISEASE

*[1]Ratna Palit, [1]Manas Ranjan Naik, [2]Divya Agarwal, [1]Karmajeet Rath, [1]Sanjay Kumar, [3]Chitta Ranjan Kar, [4]Rabindranath Sahoo and [1]Jyotsna Patnaik

[1]Department of Pharmacology, IMS & SUM Hospital, SOA University, Bhubaneswar, India
[2]Department of Anatomy, IMS & SUM Hospital, SOA University, Bhubaneswar, India
[3]Department of Nephrology, SCB Medical College, Utkal University, India, Pin 753007
[4]Department of Nephrology, I M S & SUM Hospital, SOA University, Bhubaneswar, India

ARTICLE INFO

Article History:
Received 10th January, 2013
Received in revised form
19th February, 2014
Accepted 09th March, 2014
Published online 23rd April, 2014

Key words:
Chronic Kidney Disease (CKD Stage-V),
Haemodialysis, Anaemia,
Erythropoietin, Haemoglobin.

ABSTRACT

Production of erythropoietin (EPO) is an important function of kidney. As severity of renal disease progresses, EPO level decreases and consequently anaemia progresses. In 20 healthy controls with normal renal function the serum EPO level was 13.75±1.51mIU/ml. In another 20 patients of anaemia with normal renal function serum EPO level was very high- 436.75± 224.87mIU/ml. The EPO level was highest in patients of aplastic anaemia with normal renal function-: 791.7±53.37. In CKD stage V patients with severe degree of anaemia the serum EPO level was 16.97± 2.06mIU/ml. The slight high level from the control was not sufficient enough for the degree of anaemia. However during oxidative stress the EPO level in these patients was significantly higher than the EPO level in the stable state.

INTRODUCTION

Erythropoietin (EPO) production is primarily stimulated by hypoxia, which depending on severity, increases serum EPO levels up to several hundred-fold (Ebert and Bunn 1999). One of the lesser known functions of the kidneys is the production of erythropoietin, a signalling molecule that stimulates red blood cell production, in response to decreased oxygen levels in the blood. Any disruption of this process, e.g., secondary to a functional abnormality due to Chronic Kidney Disease (CKD), has the potential to produce anaemia, a condition in which the number of circulating red blood cells, and therefore the level of haemoglobin, is lower than normal (Smith 2010). Iron deficiency anaemia (IDA) is common in CKD, affecting most patients with CKD stage 5. As the severity of renal failure increases the degree of anaemia also increases and when the patient is in end stage renal failure severe degree of anaemia is present in 100% of cases unless these patients take erythropoietin supplementation, as erythropoietin deficiency is the most common cause of anaemia in CKD. About 25% of patients with CKD needed regular blood transfusions before recombinant human recombinant erythropoietin (rHuEPO/ epoetin) became available. Transfusion therapy is an important option, and RBC transfusions are often life-saving. However, blood products also bear risks, such as the transmission of infectious diseases, acute and chronic haemolytic transfusion reactions, and transfusion-related lung injury. This was especially true for the 1980s (HIV transmission by blood and plasma derivatives) in which rHuEpo became clinically available (Wolfgang Jelkmann 2013).

The treatment of patients with chronic renal failure with recombinant human erythropoietin (rHuEPO/ epoetin) before starting or during dialysis can improve the patient's functional state, quality of life and probably the risk of morbidity and death (Ma *et al.*, 1999; Foley *et al.*,1998; Moreno *et al.*, 2000). Some studies have tried to document the level of erythropoietin (EPO) in these patients of CKD and tried to record its response to the fall of haemoglobin level. In the subcontinent no major studies have been documented regarding the level of erythropoietin in different cases of anaemia. In this study an attempt has been made to document the erythropoietin level in healthy control with no anaemia. Then the level of erythropoietin was measured in all CKD patients who had severe anaemia and had not taken either blood transfusion or erythropoietin supplementation earlier. Then some cases of anaemia of other causes were selected who had normal renal function. In these patients erythropoietin levels were assessed. In CKD patients on haemodialysis who came with pulmonary oedema the erythropoietin level was measured and compared to

Corresponding author: Ratna Palit,
Department of Pharmacology, IMS & SUM Hospital, SOA University, Bhubaneswar, India.

the erythropoietin level in these patients when they were stable and had no respiratory distress.

MATERIALS AND METHODS

Twenty healthy persons with haemoglobin level above 13gm% in males and 12 gm% in females were taken as control. They were termed as Group-A. 89 cases of CKD stage-V patients on haemodialysis who had not received earlier blood transfusion or erythropoietin supplementation or intravenous iron supplementation were termed as Group-B.Twenty cases of anaemia of other causes who had normal renal function and who did not have blood transfusion or IV iron supplementation before the study were selected and termed as Group-C. Complete Blood Count (CBC), Serum Urea, Serum Creatinine and Serum Electrolytes were estimated. Serum Erythropoietin was estimated on the first visit. It was done by chemiluminescent method. Glomerular Filtration Rate (GFR) was calculated as per CockroftGault equation. The levels of erythropoietin were compared between these three groups. In the chronic renal failure patients on dialysis, who presented with pulmonary oedema (oxidative distress) erythropoietin levels were estimated during this oxidative distress. These levels were compared statistically with the erythropoietin level in steady state. In these cases and attempt was made to see any correlation between level of hemoglobin and erythropoietin level.

RESULTS AND DISCUSSION

In the control group serum creatinine was 0.820± 0.042 mg% and GFR was 111.72±2.90 ml/min. In patients of other causes of anaemia with normal renal functions was 0.815±0.53mg% and GFR was 109.33±3.86ml/min. In CKD Stage V patients on dialysis serum creatinine was 10.498±0.35mg% and GFR was 8.12±0.021ml/min. The difference in S.creatinine between group-A & C was statistically non-significant with t = 0.087. Similarly in difference in G.F.R. between Group-A & C was non-significant with t =0.54. The patients of group-B had severe degree of renal failure with very high S.creatinine and a very low G.F.R.

In the control group the haemoglobin was 13.97±0.229gm%. In CKD Stage V haemoglobin was 6.959±0.102gm%. The difference in haemoglobin level was statistically highly significant with $p<0.01$ with t=2.74. In patients of anaemia of other causes with normal renal functions haemoglobin was 5.55±0.29gm% indicating that these patients had also severe degree of anaemia. The EPO level in control was 13.754±1.511mIU/ml, in CKD stage V it was 16.97±2.062 mIU/ml and in the patients of anaemia of other causes with normal renal functions the EPO level was 436.75±224.87mIU/ml. In the present series the serum level of EPO in CKD stage V was slightly higher than the control and

Table 1. Age and Sex distribution of patients of Control, CKD stage-V patients and other cases of anaemia with normal renal function

Age in years	Control			CKD patients Stage-V on haemodialysis			Other cases of anaemia with normal renal function		
	Male	Female	Total	Male	Female	Total	Male	Female	Total
11-20	0	1	1	0	0	0	1	0	1
21-30	5	7	12	5	1	6	9	6	15
31-40	7	0	7	9	4	13	2	1	3
41-50	0	0	0	16	5	21	0	1	1
51-60	0	0	0	23	8	31	0	0	0
61-70	0	0	0	11	4	15	0	0	0
71-80	0	0	0	3	0	3	0	0	0
Total	12	8	20	67	22	89	0	0	20

Table 2. S. Urea, S. Creatinine, GFR in different Groups

GROUPS	S.Urea (mg%)	S.Creatinine (mg%)	GFR (ml/minute)
GROUP-A(control) (n=20)	17.705±0.934	0.820±0.042	111.72±2.90
GROUP-B(CKD stage-V) (n=89)	150.421±4.21	10.498±0.35	8.12±0.021
GROUP-C (anaemia of other causes with normal renal function) (n=20)	20.7±1.064	0.815±0.053	109.33±3.86

Table 3. Haemoglobin, PCV, EPO level in different groups

GROUPS	HEMOGLOBIN (gm %)	PCV (%)	EPO LEVEL(mIU/ml)
Group-A(control) (n=20)	13.97±0.229	43.585±0.728	13.754±1.511
Group-B(CKD stage-V) (n=89)	6.959±0.102	28.811±0.370	16.97±2.062
Group-C (anaemia of other causes with normal renal function) (n=20)	5.55±0.29	24.97±0.14	436.75±224.87

Table 4. EPO level in patients of anaemia with normal renal function

Patients	EPO level (mIU/level)
Aplastic anaemia (n=4)	791.7±53.37
Sickle cell anaemia (n=2)	412.8 & 228.4
Thalassaemia (n=3)	169.8,280.6, 324.6
Anaemia due to G.I. bleed (n=6)	326.46±105.51
Anaemia of other causes (n=5)	434.56±195.99

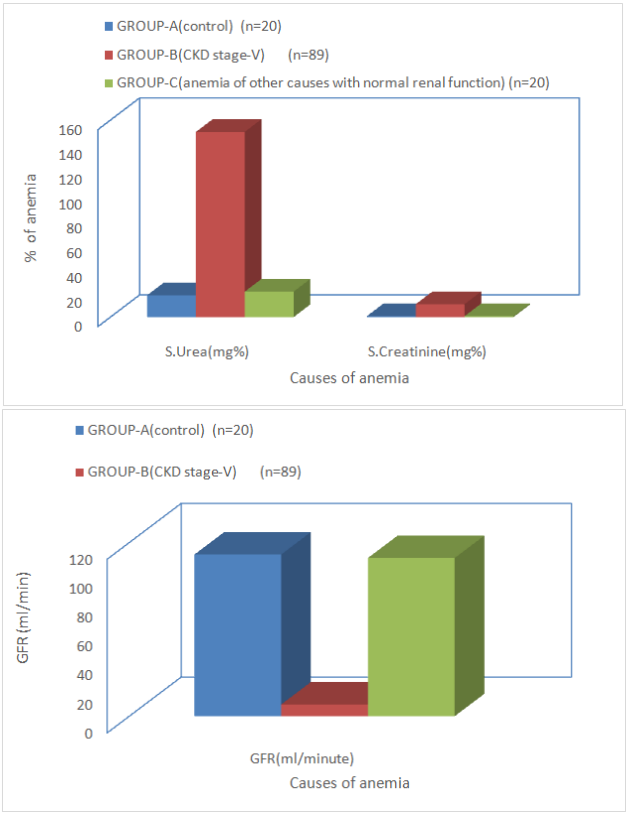

Fig. 1. S. Urea, S. Creatinine, GFR in different Groups

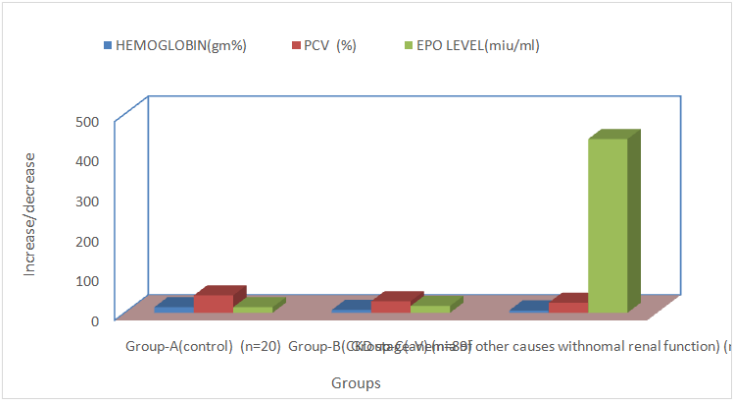

Fig. 2. Hemoglobin, PCV, EPO level in different groups

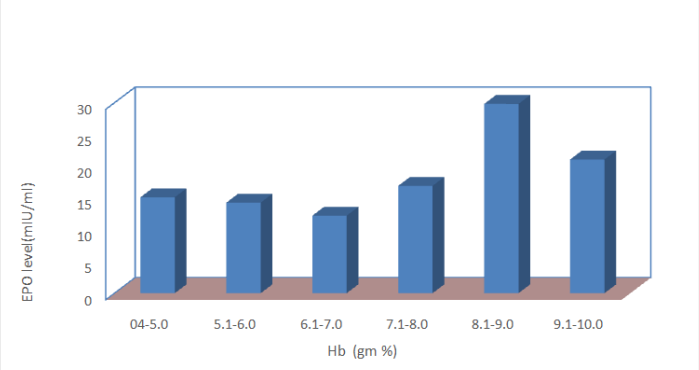

Fig. 3. Hb level and EPO level in CKD stage-v cases

the difference was statistically not significant with t=1.26. The EPO level in patients of anaemia with normal renal function was exponentially high indicating that EPO response was significant when there is normal renal function, but the response is blunted when there is renal failure. Akio Urabe et al[7] stated that in their series serum EPO level in healthy persons was 14.09±3.3mIU/ml. In their series EPO level in chronic renal failure cases with anaemia was 26.6±3.8mIU/ml. In their series EPO level in patients with iron deficiency anaemia with normal renal function was 80.3±17.3mIU/ml and in aplastic anaemia patients with normal renal function the serum EPO level was 1483.7±543.0 mIU/ml. In the present series the serum EPO level in aplastic anaemia with normal renal function it was 791.7± 53.37mIU/ml. In the sickle cell disease in two cases with normal renal function it was 412.8 and 228.4 mIU/ml, in patients of thalassemia cases (n=3), it was 169.8, 280.6 and 324.6mIU/ml respectively .In anaemia due to G.I bleed with normal renal function it was 326.46±105.51mIU/ml, and in patients of anaemia of other causes with normal renal function it was 434.56± 195.99mIU/ml. As per the findings of Akio Urabe in the present series serum EPO level was highest in patients of aplastic anaemia with normal renal function.

Table 5. Hb level and EPO level in CKD stage-v cases

Hb (gm %)	No. OF CASES	EPO LEVEL
04-5.0	1	15.1
5.1-6.0	14	14.26±11.7
6.1-7.0	28	12.20±13.95
7.1-8.0	34	16.90±20.98
8.1-9.0	10	29.8±29.55
9.1-10.0	2	21.05±6.57

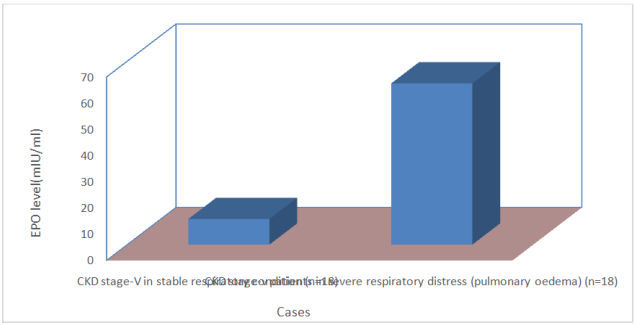

Fig. 4. CKD-V patients in respiratory distress

An attempt was made to correlate the level of EPO with the level of hemoglobin in patients of CKD stage V on dialysis. It was observed that when the patients are in CKD stage V the EPO level does not correlate with the level of haemoglobin. In the patients with haemoglobin level 4-5gm% the EPO level was 15.1mIU/ml. In patients with haemoglobin level between 5.1-6gm% the EPO level was 14.26±11.7mIU/ml, in patients with haemoglobin level between 6.1-7gm% the EPO level was 12.20±13.95mIU/ml, in patients with haemoglobin level 7.1-8.0gm% the EPO level was 16.90± 20.98mIU/ml, in patients with haemoglobin level 8.1-9.0gm% the EPO level was 29.8±29.55mIU/ml, in patients with haemoglobin level 9.1-10.0gm% the EPO level was 21.05±6.57mIU/ml. The correlation coefficient was 0.195 which was non-significant at 89 degree of freedom.

Table 6. Rise of EPO level in CKD stage-V after respiratory distress

Cases	EPO Level (mIU/ml)
CKD stage-V in stable respiratory condition (n=18)	9.76±6.72
CKD stage-v patients in severe respiratory distress (pulmonary oedema) (n=18)	61.49±7.28

Eighteen patients of CKD stage V had pulmonary oedema during some stage. The EPO level in these 18 patients during stable state was 9.76±6.72 mIU/ml. The EPO level in these patients during Respiratory Distress was 61.49±7.28mIU/ml. The difference was statistically highly significant with p<0.01with t=20.84. It is a well known fact that EPO level rises with oxidative distress.

Conclusion

In healthy persons with normal renal functions the serum EPO level depends on haemoglobin level. As the haemoglobin falls due to any reason (except CKD) the serum EPO level rises exponentially. In CKD patients stage V there is severe degree of anemia in 100% of cases unless they have received blood transfusion or EPO supplementation. However in these patients the serum EPO level does not rise with fall of haemoglobin and there is no correlation between haemoglobin and EPO level. However during oxidative stress there is significant rise of EPO level in these patients.

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