WEST AFRICAN JOURNAL OF MEDICINE

Anaemia and its Response to Treatment with Recombinant Human Erythropoietin in Chronic Kidney Disease Patients

L'anémie et sa Réponse au Traitement avec l'Humain Recombinant Erythropoietin dans les Patients de Maladie Chroniques du Rein

A. Abdu*†, F. Arogundade‡, B. Adamu†, A. I. Dutse†, A. Sanusi‡, M. U. Sani†, M. S. Mijinyawa†, A. Nalado†, A. Akinsola‡, M. M. Borodo

ABSTRACT

BACKGROUND: **The introduction of erythropoietin has transformed the management of anaemia in CKD, with considerable benefits which includes enhanced quality of life, increased exercise capacity and improved cardiac function. There is paucity of data on the beneficial effects of this treatment from this environment.**

OBJECTIVE: **The aim of this work was to study the pattern and response of anaemia and its response to treatment with recombinant human erythropoietin(r-HuEpo) in CKD patients in Nigeria.**

METHODS: **This was a prospective study in which 20 CKD patients who satisfied the inclusion criteria were recruited consecutively. Subcutaneous r-HuEpo was administered to each of the study patients, starting with a weekly dose of 50 iu/Kg and titrated according to haemoglobin (Hb) response, which was monitored fortnightly throughout the study period with the aim of achieving a target Hb of 11g/dl.**

RESULTS: **The patients studied were anaemic with mean Hb of 7.36 ± 1.05 g/dl. The anemia was normocytic normochromic in 85% of the patients. All the patients responded to treatment with r-HuEpo with the mean Hb rising from 6.74g/dl ± 0.70 to 11.64g/dl ± 0.37 and 7.64 g/dl ± 1.19 to 11.98 g/dl ± 0.45 g/dl in those on maintenance haemodialysis and pre-dialysis patients respectively. The patients reached the target Hb of 11g/dl within 8 weeks in predialytic CKD patients and within 10 weeks in those on maintenance haemodialysis.**

CONCLUSION: **Anaemia is mostly normocytic normochromic in CKD patients in our environment and r-HuEpo therapy is effective in correcting the anaemia. WAJM 2009; 28(5): 295–299.**

Keywords: **Anaemia, Chronic Kidney Disease, Recombinant Human Erythropoietin, Nigeria.**

RÉSUMÉ

CONTEXTE: *L'introduction de l'érythropoïétine a transformé la gestion de l'anémie en CKD, avec des bénéfices considérables qui inclut une amélioration de la qualité de vie, augmentation de la capacité d'exercice et la fonction cardiaque améliorée. Il existe peu de données sur les effets bénéfiques de ce traitement de cet environnement.*

OBJECTIF: *L'objectif de ce travail était d'étudier la structure et la réponse de l'anémie et la réponse au traitement avec l'érythropoïétine humaine recombinante (r-Hu EPO) chez les patients CKD au Nigeria.*

MÉTHODES: *Il s'agissait d'une étude prospective dans laquelle 20 patients CKD qui satisfaisaient aux critères d'inclusion ont été recrutés de façon consécutive. R-Hu EPO sous-cutanée a été administré à chacun des patients de l'étude, à commencer par une dose hebdomadaire de 50 UI / kg et adaptée en fonction de l'hémoglobine (Hb) de réponse, qui a été suivie de deux semaines tout au long de la période d'étude dans le but d'atteindre un objectif d'hémoglobine 11g/dl.*

RÉSULTATS: *Les patients étudiés étaient anémiques avec une moyenne de Hb de 7,36 ± 1,05 g / dl. L'anémie est normocytaire normochrome dans 85% des patients. Tous les patients ont répondu au traitement par r-Hu EPO à l'hémoglobine moyenne passant de 6.74g/dl ± 0,70 à 11.64g/dl ± 0,37 et 7,64 g / dl ± 1,19 à 11,98 g / dl ± 0,45 g / dl dans celles concernant le maintien hémodialysés et les patients pré-dialyse, respectivement. Les patients ont atteint l'objectif d'hémoglobine 11g/dl dans les 8 semaines chez les patients prédialytiques CKD et dans les 10 semaines dans les patients sous hémodialyse d'entretien.*

CONCLUSION: *L'anémie est souvent normochrome normocytaire chez les patients CKD dans notre environnement et de r-Hu EPO thérapie est efficace dans la correction de l'anémie. WAJM 2009; 28 (5): 295-299.*

Mots-clés: *anémie, l'insuffisance rénale chronique, l'érythropoïétine humaine recombinante, au Nigeria.*

†**Department of Medicine, Aminu Kano Teaching Hospital and** ‡**Renal Unit/Department of Medicine, Obafemi Awolowo University Teaching Hospital Compex, Ile-Ife**

Correspondence: Dr Aliyu Abdu, Department of Medicine, Animu Kano Teaching Hospital, PMB 3452, Kano, Nigeria

Email: aliyuabdu 2000@yahoo.co.uk

Abbreviations: CKD, Chronic kidney disease; **Hb,** Haemoglobin; **RBC,** Red blood cell; **AKTH,** Amimu Kano Teaching Hospital; **EDTA,** Ethylene diamine tetra acetic acid; **ESR,** Erythrocyte sedimentation rate; **PT,** Prothronombin time; **PTTK,** Partial thromoboplastin time kaolin; **SPSS,** Stalistical package for social science; **WBC,** White blood cell.

INTRODUCTION

Anaemia is a well recognised complication of CKD and decline in the level of Hb is noted even at early stages of the disease.[1] The principal mechanism of the anaemia is reduced production of erythropoietin by the failing kidneys, though other mechanisms such as shortened red blood cells (RBC) survival, chronic blood loss, hyperparathyroidism, bone marrow depression, iron, folate and vitamin B12 deficiencies among others do contribute. Almost every organ of the body is affected by anaemia as a result of reduced oxygen delivery and utilization in the tissues resulting in a negative impact on the QOL and contributes to multiple morbidities in these patients. Several studies have shown that recombinant human erythropoietin (r-HuEpo) is effective in correcting anaemia in CKD patients and this is associated with improvements in QOL and other comobidities such as reversal of left ventricular hypertrophy , improved measures of cognitive brain function among others.[2,3] Major practice guidelines recommend dosages in adults to be 50- 150 iu/kg/week.[4] The target Hb/ Haematocrit (Hct) level to be achieved in CKD patients on r-HuEpo has been some what controversial but a target Hb of 11g/ dl to be achieved within a period of two to four months through introduction of slow and steady increase in the Hb has been recommended.[4]

The major disadvantage in the use of r-HuEpo in this environment is that it is expensive and therefore not affordable to most patients that need it.[5,6] This study is intended to provide information on the pattern of anaemia and its response to treatment with r-HuEpo in our CKD patients.

MATERIALS AND METHODS

This prospective study was carried out at Aminu Kano Teaching Hospital (AKTH) one of the tertiary health institutions in northern Nigeria. Twenty adult CKD patients comprising ten on maintenance haemodialysis and ten with early stages of the disease not yet on haemodialysis who satisfied the inclusion criteria were recruited consecutively. The inclusion criteria were age above 16 years and CKD stage two to five with anaemia while exclusion criteria include blood transfusion in the last three months and patients already on r-HuEpo therapy. Others are presence of active infection, ureamic pericarditis, pleurisy and uncontrolled hypertension until treated as well as presence of haemo-globinopathies. Aetiological causes of the CKD were identified using validated criteria based on biochemical, and imaging information on the patient as used in previous studies.[7]

Haematological investigations were performed on five ml of blood in bottles containing potassium ethylene diamine tetra acetic acid (EDTA) for estimation of HCT, Hb concentration, RBC indices, reticulocyte count as well as white blood cell (WBC) and platelets count using coulter counter CELL DYE 3700 auto analyser. Erythrocyte sedimentation rate (ESR) was determined using westergren method.[8] Glucose six. phosphate dehydrogenase (G6PD) assay was performed using qualitative method. Haemoglobin electrophoresis, pro-thrombin time (PT), partial thrombo-plastin time with kaolin (PTTK) were done manually and bleeding time was estimated using Ivy's method as described by Dacie and Lewis.[8]

Blood samples were also taken for biochemical investigations that included serum urea, creatinine, electrolytes, calcium, phosphate, proteins, and liver function tests using auto-analyser. All the study patients also had urine microscopy, culture and sensitivity, as well as stool microscopy to look for ova or cyst of parasites. Occult blood test was carried out on stool samples collected after three days fasting from meat, fish, vegetable and iron preparation.

Human Recombinant Erythropoietin β (r-HuEpo β) was administered to the study patients by subcutaneous route starting with a dose of 50 iu/kg bodyweight weekly in two divided doses rotating the site of administration. This dosage was adjusted biweekly with an increase of 50% if the Hb rise was less than 0.3g/dl/week, and the dose was reduced by 25% if the rate of rise was more than 0.75g/dl/week, until a target Hb of 11 g/dl was reached. During the course of therapy, adequacy of dialysis was assessed monthly by measurement of Kt/V using the natural logarithm formula[9]. The r-HuEpo used was donated hence the patients received the treatment free.

Approval for the study was obtained from the ethical committee of AKTH and informed consent was obtained from each patient.

The data were analysed using the *Statistical Package for the Social Science* (SPSS), version 12.0. The analysis of continuous variables was carried out using the procedures of descriptive statistics and later, to identify any differences we used Student's t-test. Pearson's correlation coefficient was calculated to determine the correlation between numeric variables and Statistical significance was set at 0.05

RESULTS

Twenty patients were studied comprising of nine females and 11 males (M: F ratio = 1.2: 1), aged between 23 and 60 years with a mean ± SD of 41.95±10.79. The patients were in established CKD with a creatinine clearance ranging between 0.9 and 24ml/min/1.73m^2 with a mean ± SD of 9.15±8.25ml/min/1.73m^2. Diabetes mellitus, hypertension and chronic glomerulonephritis accounted for the cause of CKD in 95% of the cases. Ten of the study patients were on maintenance haemodialysis for a duration ranging from one to 12 months with a mean ± SD of 5.0±3.91months. Six patients were on three times weekly dialysis while the remaining four were on twice weekly dialysis with a Kt/V ranging between 1.10 and 1.42 with a mean of 1.24 ± 0.09 throughout the study period. Native arterio-venous fistula was the vascular access type in 60% of the patients while the remaining were using a central line using subclavian vein or jugular vein. The results of the biochemical investigations in the study patients were as shown in Table 1.

All the patients studied had anaemia, their Hb ranged between 5.6 g/ dl and 9.0 g/dl with a mean ± SD of 7.36g/ dl ± 1.05.The degree of anaemia correlated with the severity of renal impairment as a positive correlation was found between the Hb and the creatinine clearance (r=0.64 at p value of 0.001). Table 2 depicts the haematological investiga-tions results of the study patients.

Table 1: showing the results of Bio-chemical investigations in the study patients.

Parameter	Range	Mean ± SD
Creatinine (μmol/L) (58- 116)	225 – 975	459 ± 219.3
Urea (mmol/L) (1.7 – 8.3)	3.5 – 37.3	17.59 ± 9.65
Potassium (mmol /L) (3.8 – 5.4)	3.2 – 5.8	4.8 ± 0.81
Chloride (mmol/L) (98 – 108)	80 – 110	100.75 ± 8.37
Bicarbonate(mmol/L) (24 – 32)	10 – 32	19.8 ± 5.79
Sodium (mmol/L)(135 – 145)	128 – 145	134.95 ± 4.66
Calcium (mmol/L)(2.0 – 2.6)	1.0 – 2.80	1.91 ± 0.52
Phosphate (mmol/L)(0.8 – 1.6)	0.8 – 3.1	1.38 ± 0.64
Albumin (mmol/L)(35 – 52)	25.0 – 45.0	39.52 ± 4.96

Reference ranges for AKTH laboratory are shown in the bracket.

Table 2: Haematological Investigation Results in the Study Patients

Parameter	Range	Mean ± SD
Red blood cell count(4.04 – 6.13) x 10^9	2.06 – 3.12	2.73 ± 0.34
MCV (femtolitre)(80 – 97) fl	86.0 – 97.50	89.46 ± 3.95
MCH picograms(27.0 – 31.2) pg	27.00 – 31.10	29.98 ± 1.64
MCHC g/dl(31.8 – 35.4)	30.00 – 32.90	31.63 ± 1.03
Reticulocyte count %(0.5 – 1.5)	0.5 – 2.4	1.50 ± 0.94
Reticulocyte index %(0.5 – 2.5)	0.18 – 1.04	0.42 ± 0.18
WBC count X10^9/L(4 – 11 x 10^9/L)	3.60 – 10.20	6.65 ± 1.99
Platelet count x10^9/L(150- 400 x10^9/L)	81.00 – 326.0	203.65 ± 78.96
PT (seconds)(11 – 16)	15 – 24	18.4 ± 4.3
PTTK (seconds)(36 – 50)	32 – 59	41 ± 8.51
Bleeding Time (minute(2- 7)	4 – 16	9.6 ± 3.7
ESR(mm/Hr)	10 – 121	42.65 ± 34.83

MCV=mean corpuscular volume, MCH=mean corpuscular haemoglobin, MCHC= mean corpuscular haemoglobin concentration. ESR= Erythrocyte Sedimentation Rate. PT Prothrombin Time, PTTK= partial thromboplastin time with kaolin. Figures in bracket indicate reference value.

All the patients had WBC within the normal range. Majority of the patients had normal differential count while two patients had neutrophilia, one patient had lymphocytosis, and none had eosinophilia.

The blood picture was normocytic normochromic in 17(85%) of the patients while one each of the remaining patients had anisopoikilocytosis, microcytosis and macrocytosis. All the patients studied had normal G6PD status. Two of the patients had evidence of urinary tract infection. *Klebsiella spp* was grown in one of the samples while *E.coli* was grown in the other; both were successfully treated before intervention. Stool microscopy was negative for ova or cyst of helminths or other parasites while stool test for occult blood was positive in two of the patients. Blood film examination for Malaria parasite was positive in four (20%) of the patients.

All the study patients responded to the treatment with a dose dependant increase in the Hb level. The Hb rose from a mean of 6.74 ± 0.70 g/dl at the beginning of the study to 11.64 ± 0.37 g/dl in those patients on maintenance haemodialysis. While in the predialytic CKD patients, the Hb rose from a mean of 7.64 ± 1.19 g/dl to a mean of 11.98 ± 0.45 g/dl during the period of the study.

Figure 1 shows the response of the Hb to the weekly doses of the r-HuEpo in both pre dialysis and maintenance haemodialysis patients. While table III shows the weekly mean of Hb and the corresponding weekly r-HuEpo doses per kilogram bodyweight.

All the patients studied reached the target Hb of 11g/dL. Those on maintenance haemodialysis reached the target Hb in the 10th week of the study, on a mean weekly r-HuEpo dose per kg body weight of 151.88 ± 27.17i.u and no further increase in the dose was required to sustain the Hb level up to the end of the study. The predialysis patients reached the target Hb in the 8th week of the study on a mean weekly dose per kg body weight of 91.85 ± 31.12 i.u and the Hb level was sustained up to the end of the study period with no further increase in the dose. This dosage was statistically significantly lower than that of the

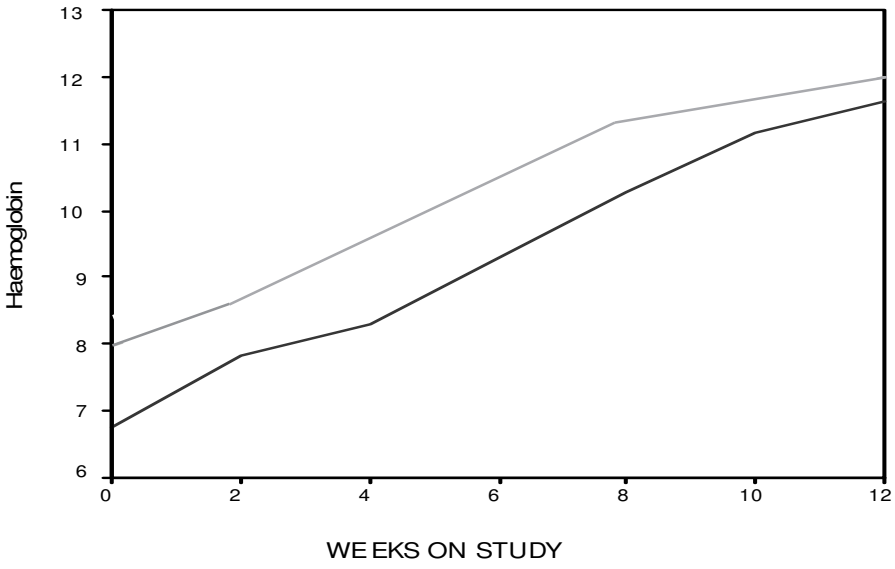

Figure 1: Response of mean weekly haemoglobin level in the study patients during the study period ——— Hemodialysis ——— Predialysis

Table 3: Mean weekly r-HuEpo dose and mean biweekly Hb throughout the study period. MHD = maintenance haemodialysis, pre HD = patients not yet requiring Haemodialysis treatment and Hb = Haemoglobin. * Indicates statistically significant difference

Week on study	Mean r-HuEpo dose in MHD patients per week	Mean r-HuEpo in pre-HD per week	Mean Hb in MHD	Mean Hb in pre-HD	P value
0	50 ± 0.00	50 ± 0.00	6.74 ± 0.70	7.99 ± 0.98	0.39
2	75 ± 0.00	75 ± 0.00	7.48 ± 0.51	8.62 ± 1.0	0.01*
4	112.5 ± 0.00	86.25 ± 18.11	8.29 ± 0.58	9.52 ± 1.24	0.01*
6	151.88 ± 27.17	91.85 ± 31.12	9.31 ± 0.84	10.42 ± 1.15	0.17
8	151.88 ± 27.17	91.85 ± 31.12	10.28 ± 0.79	11.34 ± 0.69	0.97
10	151.88 ± 27.17	91.85 ± 31.12	11.17 ± 0.75	11.70 ± 0.42	0.15
12	151.88 ± 27.17	91.85 ± 31.12	11.64 ± 0.36	11.98 ± 0.45	0.93

patients on haemodialysis with a p value of 0.001.

One of the patients on maintenance haemodialysis had an episode of hypertensive encephalopathy during the eight week of the study, which was successfully treated. All the patients needed adjustment in their anti hypertensive medication to maintain adequate blood pressure control during the study period.

DISCUSSION

The management of anaemia in CKD has been transformed since the licensing of r-HuEpo in 1988 in the US. Studies have shown that vast majority of patients respond to treatment with an increase in Hb level associated with considerable benefits, including enhanced quality of life, increased exercise capacity and improved cardiac function.[8]

All the patients studied had anaemia and this finding is consistent with the findings of other investigators in Nigeria.[11–13] This confirms the high prevalence of anaemia among chronic kidney disease patients in our environment. Although previous studies in Nigeria did not differentiate between those on dialysis and predialysis patients, we found anaemia to be more severe in patients on maintenance haemodialysis than those with early CKD who are not yet on haemodialysis. This may be due to the effect of residual renal function as the creatinine clearance is higher in the predialysis patients. This study and those by others[11,13,14] have shown that there is a positive correlation between the degree of anaemia and the severity of the renal impairment. This may be due to reduced production of erythropoietin by the failing kidneys and also presence of uraemic inhibitors of erythropoiesis.

The anaemia in the study group was hypoproliferative as evidenced by the low RBC count and reduced reticulocyte index, consistent with the findings of other workers. [11,13,14] Similarly, the blood picture was normocytic, normochromic in the majority of patients in this study, which is in agreement with the findings by other workers.[11,13,14,] The WBC, platelet counts and bleeding time were all within normal ranges in the patients studied, which is in keeping with findings by others. [11–14] The normal WBC count may be due to the fact that uraemia affects the functions of the leucocytes rather than granulopoiesis and studies have shown that there is poor leucocytes response to infection.[15] This may explain the occurrence of urinary tract infection in two of the studied patients.

Uraemia is associated with functional abnormality of the platelets manifested by prolonged bleeding time. However, in this study there was no correlation between bleeding time and severity of renal impairment as measured by the creatinine clearance. This is similar to finding by Remuzzi et al [16] though is at variance with the findings by other workers, [11,14] who reported a positive correlation between serum creatinine and the bleeding time. This finding is not surprising as there are other factors known to affect bleeding time in uraemia apart from abnormal platelet function. The PT, PTTK in this study was also found to be within normal range. Thus bleeding diathesis could not have contributed significantly to the anaemia seen in these patients.The erythrocyte sedimentation rate was increased in the studied patients, which could indicate the presence of an inflammatory process. The ESR has been shown to be an indicator of chronic inflammatory activity, which is simple and inexpensive though its usefulness is limited by its low sensitivity and specificity.[17]

All the patients studied responded to treatment with r-HuEpo and all the patients achieved the target haemoglobin of 11g/dl. This is similar to previous reports which showed that r-HuEpo corrects anaemia in dialysis patients [18,19] and in predialysis CKD patients [20]. Arogundade et al [13] reported that 70% of the patients they treated with r-HuEpo achieved the target haematocrit of 33% and they found causes of poor response in others to include inadequate dialysis, iron deficiency and under dosing. In this study dosages were given according to the Hb response as recommended by the major practice guidelines[4,21] unlike the dosage regimens used by Arogundade et al of initial 2000 iu to 4000 iu three times weekly. None of the patients had poor response; this may be due to the fact that most of the known causes of r-HuEpo hyporesponsiveness were taken care of in the studied population. For example, all the patients were screened and treated appropriately for infection, adequacy of haemodialysis was closely monitored and ensured throughout the study period. However other known causes of hyporesponsiveness such as hyperparathyroidism, folate and B-12 deficiencies were not assessed.

The patients reached the target Hb at dose within the ranges recommended by major practice guidelines[4,21] i.e. dosages of 50–150iu/kg/week. Conlon *et al* [22] reported that in the patients they studied, those on maintenance haemodialysis reached the target haemoglobin at a mean r-HuEpo dose of 125 i.u /kg/week. This study has shown that predialysis CKD patients reached the target Hb within a mean r-HuEpo dosage of 91 iu/kg/week, which is relatively lower

than the dosage of 151iu/kg/week on which those on maintenance haemodialysis reached the target Hb. This may be due to residual renal function in predialysis patients, as it has been shown in this study as well as others that the degree of anaemia correlates with the level of renal function another factor is the possible blood losses during the dialysis procedure.

The patients reached the target Hb within a period of eight weeks in predialysis and ten weeks in those on maintenance haemodialysis. This period is similar to the findings by others.[18-19,20,22]

Hypertension is a frequent complication of CKD as well as a recognized complication of r-HuEpo therapy. It was the major cause of CKD in 35% of patients in this study. Four patients (20%) required initiation of antihypertensive medication in this study and another 60% required an increase in their antihypertensive medication and blood pressure control was monitored throughout the study period. However one of the patients on maintenance haemodialysis developed hypertensive encephalopathy at the eight weeks of treatment, which necessitated admission into the hospital and was successfully treated. The finding of hypertensive encephalopathy complicating r-HuEpo treatment was previously reported. [23] This implies that, blood pressure control should be carefully monitored and ensured in all patients on r-HuEpo treatment.

No thrombosis of the vascular access was noted in the six maintenance haemodialysis patients with native arteriovenous fistula during the period of the study. Eschbach et al [18] reported a thrombotic event rate of 0.3/year in patients treated with r-HuEpo, which was similar to rate of 0.5 events/year in haemodialysis patients not treated with r-HuEpo. Conlon et al [20] reported that 7% of their patients on maintenance haemodialysis developed thrombosis of their AV fistula.

Conclusion

Anaemia in CKD patients is mostly normocytic normochromic in our setting. Therapy with r-HuEpo at doses of 150iu/kg body weight 91iu/ kg in haemodialysis and predialysis patients respectively, is effective in correcting the anaemia in CKD patients in our setting comparable to the recommended dosages suggested in major practice guidelines. We therefore recommend the use of r-HuEpo in anaemic CKD patients who can afford the treatment and careful monitoring of known causes of hypo responsiveness to this treatment is advised.

ACKNOWLEDGMENT

We are grateful to SWIPA pharmaceuticals Nigeria plc for supplying most of the r-HuEpo used in this study. We also thank Mr Ameh Sunny of Chi Pharmaceuticals for some logistic support.

REFERENCES:

1. Levin A. Prevalence of cardiovascular damage in early renal disease *Nephrol Dial transplant* 2001; **16:** 7–11.
2. Fisher JW. Erythropoietin: Physiology and Pharmacology Update. *Exp Biol Med* 2003; **228:** 1–14.
3. Wolcott DL, Marsh JT, La Rue A, Carr C, Nissenson AR. Recombinant Human Erythropoietin Treatment May Improve Quality of Life and Cognitive Function in Chronic Renal Failure Patients; *Am J Kidney Dis* 1989; **14:** 478–485.
4. Revised European Best Practice guidelines for the management of anaemia in patients with chronic kidney disease. *Nephrol Dial Transplant* 2004; **19:** 1-II47.
5. Ojo-Oziegbe, Oviasu E. Rheological effects of recombinant human erythropoietin in chronic renal failure patients Benin City. 15th Annual Scientific Conference of Nigerian Association of Nephrology Book of Abstract 2003; page19–20.
6. Hedi BM, Ezzeddine A, Karim Z. Anaemia and end stage renal disease in developing world. *Artificial organ* 2002; **26:** 760–764.
7. Akinsola W, Odesanmi W O, Ogunniyi JO, and Ladipo GO. Diseases causing renal failure in Nigerians- prospective study of 100 cases. *Afr Journal Med, Med Sci* 1989; **18:** 131–135.
8. Dacie JV, Lewis SM (Eds) Practical Haematology. Sixth edition. Churchill living stone 1984.pp 122–125.
9. Francesco locatelli. Epoetin beta and optimal anaemia management in renal disease, pocket Pharma. London. Science Press Ltd. 2004.
10. Moreno F, Sanz-Gvajando D, Lopez-Gomez JM, Jofre F, and Valderrabano F: Increasing the haematocrit has beneficial effect on quality of life and is safe in selected haemodialysis patients. *J Am Soc Nephrol* 2000; **11:** 335–342.
11. Akinsola A, Durosinmi MO, Akinola NO. The Haematological profile of Nigerians with Chronic Renal Failure; *Afr J Med Med Sci* 2000; **29:**13–16.
12. Oluboyede O.A, Williams A.I.O. Serum Ferritin and other iron indices in adult Nigerians with chronic renal failure: Review of management of anaemia. *Afri J Med Med Sci* 1995; **24:** 231–237.
13. Arogundade F.A.Bappa A, Sanusi AA, Akinola NO, Adediran JA and Akinsola A. Haematologic indices and the response to erythropoietin in Chronic Renal Failure. *Trop J Nephrol* 2006; **1:** 13–20.
14. Bappa A. Anaemia in Nigerians with chronic renal failure (Part II dissertation). West African College of Physicians; April 2001.
15. Chonchol M. Neutrophil dysfunction and infection risk in ESRD. *Semin Dial* 2006; **19:** 291–296.
16. Remuzzi G, Livio E, Marchiaro G et al. Bleeding in renal failure: Altered platelet function only partially corrected by haemodialysis. *Nephron* 1978; **22:** 347–353.
17. Brigden ML. Clinical Utility of the Erythrocyte Sedimentation rate. *Am Fam Physician* 1999; **60:** 1443–50.
18. Eschbach JW, Abdulhadi MH, Browne JK, Delano BG, Downing JC, Egrie RW *et al.* Recombinant Human Erythropoietin in Anaemic patients with end stage renal failure. Results of a phase III multicenter clinical trial. *Ann Intern Med* 1989; **111:** 992–1000.
19. Winearls CG, Oliver DO, Pippard MJ, Reid C, Downing MR, Cotes PM et al. Effect of human erythropoietin derived from recombinant DNA on the anaemia of patients maintained by chronic haemodialysis. *The Lancet* 1986; **2:** 1175–1178.
20. Lim VS, Gowin D, Zabala D. Recombinant Human Erythropoietin Treatment in pre-Dialysis patients. *Ann Intern Med* 1989; **110:** 108–114.
21. NKF-K/DOQI Clinical Practice Guidelines for Anaemia of Chronic Kidney Disease Update 2000. *Am J Kidney Dis* 2001; **37:** 182–238.
22. Conlon PJ, Walshe JJ, O' Donohoe A. The use of recombinant erythropoietin in end stage renal disease. *Ir J Med Sci*. 1993; **162:** 17–19.
23. Novak BL, Force RW, Munford BT, Solbrig RM, Rona DO, Solbrid M. Erythropoietin induced hypertensive urgency in a patient with chronic renal insufficiency: case report and review of the literature. *Pharmacotherapy* 2003; **23:** 265.