Prevalence of Anaemia and other Haematologic Derangements in End Stage Renal Disease Patients in the University of Port Harcourt Teaching Hospital

FS Wokoma and PC Emem-Chioma

Renal Unit, Department of Medicine, University of Port Harcourt Teaching Hospital, PMB 6173, Port Harcourt, Nigeria

ABSTRACT

Anaemia and other haematologic derangements are common in patients with chronic kidney disease (CKD), especially end stage renal disease (ESRD). Anaemia is an independent risk factor for cardiovascular morbidity and mortality in CKD. The prevalence of anaemia and other haematologic derangements in the population of ESRD patients at the University of Port Harcourt Teaching hospital (UPTH) is not known.The objective of the study is to determine the prevalence of anaemia and other haematologic derangements in dialysis naive end stage renal disease patients in the University of Port Harcourt Teaching Hospital. A retrospective analysis of the haematologic indices of pre-dialysis end stage kidney disease patients at the UPTH from January to December 2007 was done. There were seventy patients, 50 males, 20 females (M/F= 2.5:1), mean age of 44 $\pm$ 17.0(18-85) years and mean e-GFR of 7.1 $\pm$ 2.1(3.5-10.8)mls/min. They had a mean haematocrit of 22.8 $\pm$ 3.1(10-38) percent, mean haemoglobin concentration of 8.8 $\pm$ 3.1(3.3-16)g/dl. Others were mean ESR, 93.1 $\pm$ 45.1(7-136)mm/hr, mean peripheral total leukocyte count 7,533.5 $\pm$ 3,949.6(2,499-18,800)/mm^3 and a mean platelet count 145,000 $\pm$66,500.1 (60,000-240,000)./mm^3 . Anemia was the dominant haematologic abnormality occurring in 66(94.3%) patients. Moderate to severe anaemia occurred in 58 (82.9%) of the patients, 6 (8.6%) had haemoglobin levels within normal range. Twelve patients (17%) had leukocytosis and 2(2.9%) had leukopenia. Peripheral blood film showed evidence of iron deficiency and some abnormal cells. The e-GFR of the patients showed positive correlation with haematocrit (r= +0.2) and haemoglobin(r= +0.1) level respectively. Blood urea and serum creatinine showed negative correlation with haematocrit(r = -0.2) and haemoglobin concentration(r = -0.2) respectively. In conclusion, we found that anaemia was the dominant haematologic abnormality in dialysis naive end stage renal disease patients in the University of Port Harcourt Teaching hospital. Both haematocrit and haemoglobin levels showed positive correlation with e-GFR. The findings are consistent with previous studies. Considering that anaemia is a risk factor for morbidity and mortality in ESRD patients, there is need for increased attention to the correction of anaemia in ESRD patients in Nigeria and other resource poor countries.

Keywords: *Haematologic abnormalities, end stage renal disease, University of Port Harcourt Teaching hospital*

Corresponding author : **Dr P.C. Emem-Chioma**

Renal Unit, Department of Medicine, University of Port Harcourt Teaching Hospital, PMB 6173, Port Harcourt. E-mail:emem.chioma2008@gmail.com. Tel: 0803 310 3653

INTRODUCTION

Derangements in haematologic indices, especially anaemia, are common in patients with chronic kidney disease (CKD) and chronic kidney failure. The subject has been extensively studied globally [1-3] and to some extent, in Nigerian patients with CKD [4,5]. Whereas, the other haematologic derangements are generally minor and of less clinical importance, anaemia remains the dominant abnormality that is of significant clinical implications for the CKD patient.

The degree of anaemia worsens as the chronic kidney disease progresses. Anaemia becomes profound as the glomerular filtration rate (GFR) drops to about 30ml/min/1.73m ^{2} and worsens as CKD progresses towards end stage kidney disease [1].

Anaemia contributes significantly to the high morbidity and mortality associated with advanced CKD, especially in poor countries, where maintenance dialysis is sub-optimal and access to erythropoietin is very low [5, 6]. Anaemia is an independent risk factor for cardiovascular morbidity and mortality in CKD patients by inducing volume overload, left ventricular dilatation and left ventricular hypertrophy [7, 8].

In the University of Port Harcourt Teaching hospital, there has been no previous study of the problem of haematologic disorders in chronic kidney disease. This study therefore, seeks to determine the prevalence of anaemia and other haematologic indices of end-stage kidney disease patients before commencement of long term haemodialysis program. The results are intended to determine the magnitude of the problem in our facility, establish a base data on the subject in the hospital as well as contribute to the National data on the subject.

Aims and Objectives

To determine the prevalence and distribution of anaemia and other haematologic abnormalities in dialysis naive end stage renal disease patients at the University of Port Harcourt Teaching Hospital (UPTH).

METHODS

The study was a retrospective analysis of data of haematologic indices in CKD- 5 patients before commencement of maintenance dialysis in UPTH. The clinical case files of patients presenting between January and December 2007 were studied. The results of the first series of laboratory tests performed at first presentation before their first haemodialysis session were used for analysis.

Data extracted from the clinical case files include the bio-demographic data, date at first diagnosis of chronic kidney disease(CKD), the primary renal diagnosis, the pre-dialysis biochemical parameters namely, plasma concentrations of sodium, potassium, bicarbonate, urea, creatinine, total protein and albumin as well as the estimated glomerular filtration rate (e-GFR) . The pre-dialysis peripheral haematologic indices analyzed include , the haematocrit, the haemoglobin concentration(Hb), erythrocyte sedimentation rate(ESR), the total peripheral leukocyte count(TWBC), the percentage differential leukocyte counts, the platelet count as well as the peripheral blood film report.

National kidney foundation/kidney dialysis quality of life index (NKF/KDOQI) guidelines[9] on definition of anaema in CKD was adopted, which defines anaemia as a haematocrit level of 36% percent or less, or an haemoglobin concentration of 12g/dl or less. The degree of anaemia was categorized as mild (Hct.30- 36%; Hb.10-12/dl), moderate (Hct. 21-29.9%; Hb 7-9.9g/dl) or severe (Hct. less<21%; Hb <7g/dl) respectively. Leukocytosis was defined as a total peripheral leukocyte count of >11,000/mm^3 of blood, while leucopenia was defined as a total peripheral leukocyte count of 3000/mm^3 of blood or less. Eosinophila was defined as peripheral eosinophil percentage of 10% or higher. Thrombocytosis was defined as the total peripheral platelet count of more than 400,000/mm^3 of blood while thrombocytopenia was defined as total peripheral platelet count of less than 100,000/mm^3. Erythrocyte sedimentation rate of 20 mm/hour (Westergren) or more was taken as elevated [10].

All the tests for the haematologic and biochemical parameters were performed in the central laboratory service of the hospital.

Chronic kidney failure was defined and staged in accordance with the NKF/ KDOQI guidelines11 for the diagnosis and staging of chronic kidney disorder. The estimated GFR (e-GFR) was calculated using the Cockcroft and Gault [12] formula for estimation of GFR.

Study Population

All patients with end stage kidney disease, who commenced maintenance haemodialysis in the hospital during the study period, January to December 2007.

Exclusion

Patients with major primary haematologic disorders such as the major haemoglobinopathies, leukemia, lymphomas and other infiltrative disorders were excluded. Others include those with evidence of any other obvious major causes of anaemia, other than CKD, as well as evidence of recent blood transfusions and or recent treatment with erythropoietin. Patients with evidence of previous dialysis were also excluded.

Data Analysis

The data were analyzed using Statistical package for social sciences (SPSS- version6). Quantitave variables are presented as mean ± standard deviation. Pearson correlation coefficient(r) was used to determine the relationship between dependent variables. Student t-test was applied to determine the measures of significance between sub populations with the level of significance (p-value) set at 0.05. Tables were used as appropriate.

Study Limitations

Being a retrospective study, it was not possible to exclude patients with all other possible causes of haematologic disorders, other than those that could easily be identified from the patients' records. Similarly, more detailed haematologic indices such as mean corpuscular volume (MCV), mean haemoglobin concentration (MCHC), leukocyte function studies, iron studies and bone marrow studies were not available for study. These tests are usually not part of the routine haematologic assessment tests for pre-dialysis CKD patients in our center.

RESULTS

The data for seventy patients were suitable for analysis. They constitute 50 males and 20 females giving a male to female ratio of 2.5:1. Their ages ranged from 18 t0 85 years with a mean age of 44.2 ±17.0 years. Their e-GFR ranged from 3.50 to 10.8 ml/min with a mean of 7.1 ± 2.1ml/min. Their hematologic and biochemical profiles before commencement of first dialysis at are detailed in tables 1 and 2.Their mean haematocrit was 22.8 ± 3.1(10-38)percent , while the mean haemoglobin concentration was 8.8 ± 3.1(3.3-16) g/dl respectively. The erythrocyte sedimentation rate ranged from 7 to 136mm/hr, with a mean of 93.1 ± 45.1 mm/hr. The mean total leukocyte count was 7,533.5 ±3,949.6(2,499-18,800)/mm^3. The platelet counts ranged from 65,000 to 240,000/mm^3 with a mean of 145,000 ± 66,500.1/mm^3.

The frequencies of abnormalities of the haematologic indices are shown in table 3. Sixty eight patients (97.1%) had haematocrit levels of 36% or less, while 64(91.4%) had haemoglobin concentration levels of 12g/dl or less. Thus an aggregate of 66(94.3%) of the patients were anaemic. Twelve patients (17.1%) each had mild anaemia by haematocrit or haemoglobin estimation. Thirty-six patients (51.4%) had moderate anemia by haematocrit and 32(45.7%) by haemoglobin estimation, while severe anemia was observed in 22(31.4%) by haematocrit and 26(37.1%) by haemoglobin concentration respectively. The differences between haematocrit and haemoglobin values were not statistically significant ($p>0.05$). Six patients (8.6%) had haemoglobin and haematocrit levels that were within normal limits.

Fifty-six patients (80%) had erythrocyte sedimentation rate >20mm/hr. Leukocytosis of > 11,000/mm^3 was observed in 12(17.1%) of the patients, while leucopenia of < 3000/ml was observed in 2(2.9%). Eosinophilia of > 10% was observed in 8(11.4%) of the patients. Ten (14.3%) had

Table 1: Haematologic profiles of the patients

Haematologic parameters	Range	Mean ± sd
Haematocrit.(%)	10-38	22.8 ± 3.1
Haemoglobin conc.(g/dl)	3.3-16	8.8 ± 3.1
*ESR(mm/hr)	7-136	93.1 ± 45.1
Total white cell count.(/mm^3)	2400-18,800	7,533.5 ±3,949.6
Neutrophil %	26-96	66.1 ± 15.1
Lymphocyte%	4.0-70	29.1 ±13.1
Eosinophil%	3.0-19	5.6 ±5.1
Platelet count(/mm^3)	65,000-240,000.0	145,000 ±66,500.1

**ESR- Erythrocyte sedimentation rate (mm-hour Westergren)*

Table 2: Biochemical profiles of the patients

Biochemical parameters	Range	Mean ± sd
Sodium(mmol/l)	119-146	133.2 ± 7.0
Potassium(mmol/l)	3.3-8.0	5.3 ±1.4
Bicarbonate(mmol/l)	12-26	17.8 ± 3.3
Urea(mmol/l)	20-88.5	36.6 ± 18.7
Creatinine(umol/l)	645-2102	1110.6 ± 533.3
Total protein(g/dl)	42-87	60.7 ± 12.1
Albumin(g/dl)	12-66	31.3 ± 12.4
Fasting blood glucose(mmol/l)	2.2-24	5.7 ±4.7

thrombocytopenia and none of the patients had thrombocytosis.

Table 3: Abnormal haematologic indices

Haematologic abnormality	No.	Percentage
Haematocrit. <36%.	69	98.6
Anaemia(Hb <12g/dl)	64	91.4
High ESR(>20mm/hr)	56	80.0
Leukocytosis(>11,000/mm^3)	12	17.1
Leukopenia(<3000/mm^3)	2	2.9
Neutrophilia%(>70%)	24	34.2
Neutropenia%(<25%)	nil	0.0
Eosinophilia(>10%)	8	11.4
Thrombocytopenia(<100,000/mm^3)	nil	14.3
Thrombocytosis(>400,000.0/mm^3)	nil	0.0

The peripheral blood film showed some abnormalities (table 4). Microcytosis 12(17.1%), hypochromic red cells 8(11.4%) and microcytic-hypochromic red cells 6 (8.5%) consistent with iron deficiency anaemia were the commonest. Burr cells (crenated red cells) sometimes called renal failure cells were reported in 6(8.6%) patients , while toxic neutrophils suggestive of serious infections were reported in 4(5.7%).

Table 4: Abnormal blood film findings

Abnormal blood film.	No. of patients	Percentage
Burr cells	6	8.6
Codocytes	4	5.7
Microcytic red cells	12	17.1
Hypochromic red cells	8	11.4
4Hypochromic-microcytic	6	8.6
Poikilocytes	4	5.7
Anisocytes	8	11.4
Toxic neutrophils	4	5.7

The biochemical parameters were consistent with features of advanced kidney failure (table 2). All the patients had e-GFR values less than 15mls per minute, values consistent with end stage renal disease. The mean e-GFR was 7.1± 2.1(3.5-10.8) mls/min. The e-GFR showed positive correlation with haematocrit (r= +0.2), haemoglobin concentration (r= +0.1), platelet count(r = +0.5) and total Leukocyte count(r=+0.2) respectively.

DISCUSSION

Anaemia was the most significant haematologic abnormality occurring in 94.3% of the patients, followed by high ESR, peripheral eosinophilia and leukocytosis. The peripheral blood film showed evidence of iron deficiency anaemia and some abnormal cells such as burr cells, codocytes and toxic neutrophils.

The high prevalence of anemia as the dominant haematologic abnormality is consistent with previous studies of the haematology of CKD worldwide and in Nigeria [1, 3, 4, 5]. In terms of severity, majority of the patients (82.8 %) had moderate to severe anaemia. Six patients (8.6%) however had haemoglobin levels within normal limits. No case of polycythaemia was observed.

The findings of normal hemoglobin/haematocrit levels in six patients with stage 5 CKD was not expected, however there have been reports of polycythaemia in patients with CKD as well as among maintenance dialysis patients . Polycythaemia

have been reported in CKD due to hydronephrosis, polycystic kidney disease, dialysis patients who developed simple renal cysts and renal tumours [13-15]. Local ischaemia and eythropoetin expressing tumour cells are said to be responsible. Some post transplant CKD patients also manifest polycythaemia. Such polycythaemia is said to result from an excessive activity of the erythropoietin producing tissue in the transplant kidney in response to the pre-transplant anaemic state of the recipient [3, 16] Two of our patients had polycystic kidney disease, three had obstructive uropathy, but none of these had normal or elevated haematocrit levels.

Though the causes of anaemia in CKD patients are often multifactorial, the deficiency of the production of erythropoietin by the diseased kidneys remains dominant and most important [1]. Erythropoietin, a glycoprotein growth factor is produced by the peri- tubular fibroblasts within the renal cortex. Erythropoietin promotes the proliferation and the terminal differentiation of erythrocyte precursor cells into normoblasts and subsequently into mature erythrocytes [3]. The low erythropoietin level in CKD leads to deficiency of bone marrow erythropoiesis which results in anemia.

Several studies have demonstrated the strong relationship between the progression of chronic kidney disease and anaemia. Though the relationship is not linear, in most studies [17, 18] a positive correlation between the GFR and haemoglobin or haematocrit levels have been demonstrated in patients with CKD as was the case in this study. Similarly serum creatinine levels show negative correlation with haematocrit or haemoglobin concentration as was the case in this study. Most patients with CKD become profoundly anaemic as the e-GFR drops to 30 mls /min or below.

Anemia induces significant hypoxaemic injury to the tissues as well as a serious haemodynamic stress to the patient's cardiovascular system. Anaemia is an independent risk factor for left ventricular hypertrophy(LVH), left ventricular dilatation and death independent of hypertension in patients with CKD, thus contributes to the high cardiovascular morbidity and mortality observed in CKD patients [7, 8].

As observed in this study, moderate to severe anemia is a common presenting feature in dialysis populations in Nigeria [4, 5]. Though there are no studies linking dialysis outcomes with anemia in Nigeria, it is quite plausible that anaemia account to a large extent, for the poor clinical state at presentation for dialysis and the poor dialysis outcomes as reported from centers across Nigeria [4-6, 19-21]. Such clinical state is often characterized by the presence of moderate to severe anaemia, hypertension, haemodynamic instability, gross oedema, volume overload and pulmonary oedema. In most instances the first haemodialysis session constitute an emergency life rescue procedure as a result of haemodynamic instability. Most patients receive two to three units of blood during their first dialysis session.

The optimal control of anaemia in CKD, has been demonstrated in several studies to significantly improve the symptoms, exercise tolerance, functional ability, dialysis outcomes and the overall quality of life of CKD patients worldwide [22,23]. For this reason international guidelines have been developed for the management of anaemia in CKD patients [24, 25]. Earlier advocacy was for the normalization of haematocrit, but recent reports, however have shown that such normalization is associated with poor outcomes in patients with CKD. For this reason, NKF/KDOQI [26] in 2006 recommended the target haemoglobin levels of between 11 and 12 g/dl as optimal for CKD patients.

Recombinant human erythropoietin (r-HuEPO) is the gold standard for the management of anaemia of CKD and has demonstrated wide clinical success and acceptability globally [27, 28]. The correction of anaemia with r-HuEPO in CKD patients has contributed significantly to the better outcome and longevity of maintenance dialysis patients especially in the developed countries of the world, where ready access and optimal treatment is the norm.

Unfortunately in Nigeria, recombinant human erythropoietin is quite expensive and not within reach of majority of CKD patients. Arogundade et al [5] in a study of thirty newly diagnosed CKD patients showed that only 33.3% could afford erythropoietin therapy for three months. In our center (unpublished data) not up to ten percent receive erythropoietn, even then very irregularly. This picture is likely to be the same across the country. Erythropoietin adds extra heavy financial burden on the resource poor patients in our practice environment. The high cost of haemodialysis treatment and high cost of erythropoietin make optimal treatment of CKD patients in resource poor settings like Nigeria almost an impossible task, in the absence of any form of government or social security support. Access to

regular erythropoietin for optimal control of anaemia and access to optimal dialysis remain one of the greatest challenge facing renal care providers and CKD patients in Nigeria and other resource poor sub-Saharan African nations.

Repeated blood transfusions are not a viable alternative to erythropoietin. Blood transfusions add more nitrogenous impurities to the body of the uraemic patient. Also, blood for transfusion is increasingly becoming scarce and expensive. The risk of transmission of deadly blood borne infections is a reality in spite of pre-transfusion screening, while repeated transfusions may lead to the development of HLA antibodies [29]. From the foregoing therefore, recombinant erythropoietin remain the treatment of choice for anaemia in CKD every where in the world. Government driven intervention that will ensure the regular access to erythropoeisis stimulating agents (ESA) and dialysis in the care of patients with End stage kidney failure becomes inevitable in resource poor countries such as Nigeria and other sub-Saharan African countries.

Abnormalities in the other haematologic indices studied were few. The high rate of elevated erythrocyte sedimentation rates (ESR) could be explained by the high rate of anaemia and the evidence of possible infections in the patients. ESR values had negative correlation with both haematocrit and haemoglobin levels'(r=-0.3, and -0.4 respectively). The presence of neutrophilia (34.2%) and toxic neutrophils (5.2%) in the peripheral blood film of some of the patients is a reflection of the possible presence of pyogenic infections. With the exception of eight patients (11.4%) with leucocytosis, from whose urine organisms were cultured, there was no documented evidence of specific infections in any of the organ systems, to account for the leucocytosis. It is however possible that the patients with polycystic kidney disease and obstructive uropathy may harbour occult infections that could account for the leucocytosis.

We could not determine the exact cause of the 11% eosinophlia we found in the patients. The records could not provide any evidence of history of allergy, or intestinal and systemic parasitic infestations. It is quite possible the eosinophilia may have been due to intestinal parasitic infestations such as hook-worm infestations, which are prevalent in the tropical environment as ours. Exposure to angiotensin converting enzyme (ACE) inhibitors may be a factor as most of the patients, were on ACE-inhibitors used for their anti-hypertensive and reno-protective properties. Since the study data were pre-dialysis data, dialyser membrane (e.g. AN69) induced anaphylactic reactions was unlikely.

Though 14.3% of the patients had thrombocytopenia with platelet counts of less than 100,000.0/mm^3, none of the patients manifested clinical features of haemorrhagic diathesis. There was no record of excessive bleeding during haemodialyis sessions in spite of heparin dialysis. The absence of spontaneous bleeding in these patients may be because none of them had thrombocytopenia below 50,000.0/mm^3. Some studies have demonstrated that functional platelet abnormalities tend to predominate in uraemic patients[30, 31] .

The peripheral blood film of our patients showed some abnormal cells (table4). The presence of microcytes, hypochromia and microcytic-hypochromia were indicative of iron deficiency, which is common in CKD patients [28, 31]. Causes of iron deficiency in CKD patients are multi-factorial and include poor dietary iron intake, chronic gastrointestinal blood loss, intestinal infestations, as well as blood loss from dialysis. Iron studies and bone marrow iron staining were however not done to confirm iron deficiency state in these patients. The presence of iron deficiency is however of significant relevance for effective treatment of the anaemia of CKD with erythropoietin. In the absence of iron, recombinant human erythropoietin will not be effective, as haem would not be incorporated into the haemoglobin molecule. For optimal response to erythropoietin therapy the iron deficit in renal anemia must be determined and corrected with parenteral iron to replenish the iron stores during erythropoietin therapy. There are international guidelines [26] for iron therapy in CKD patients. Burr cells and codocytes are commonly found in the peripheral blood film of chronic renal patients and are sometimes called renal failure cells, but they are not pathognomonic of chronic renal failure[31].

CONCLUSION

This study as in previous local and international studies confirm anaemia as the dominant and most important haematologic derangement in patients with end stage renal disease. Moderate to severe anaemia is most prevalent in our patients. The role of anemia as a major risk factor for poor outcomes in CKD patients in Nigeria and similar resource poor settings are

discussed. The central role of optimal erythropoietin therapy in reversing the deleterious effects of anaemia, and improving outcomes in CKD patients is well established. Poor access to optimal erythropoietin therapy and optimal dialysis remains one of the most important challenges facing renal care in Nigeria.

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