International Journal of Clinical Medicine Research
2017; 4(5): 51-55
http://www.aascit.org/journal/ijcmr
ISSN: 2375-3838

American Association for Science and Technology


**Keywords**
Sickle Cell,
Vaso-occlusive Crisis,
Steady State,
Haemoglobinopathy

Received: April 23, 2017
Accepted: May 5, 2017
Published: August 29, 2017

# Comparative Haematological Evaluation of Sickle Cell Anaemic Patients in Steady State and During Vaso-occlusive Crisis at Maiduguri, Nigeria

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## Citation

Usman A Abjah, Jessy T Medugu, Haruna Ayuba Bulama, Idris Abdullahi Nasir, John Kankop Wakbe, Ghapouen Amed Bachir Peyou. Comparative Haematological Evaluation of Sickle Cell Anaemic Patients in Steady State and During Vaso-occlusive Crisis at Maiduguri, Nigeria. *International Journal of Clinical Medicine Research*. Vol. 4, No. 5, 2017, pp. 51-55.

## Abstract

*Background:* Sickle cell disease (SCD) is a hereditary haemoglobinopathy characterized by deranged haematopoiesis, and intermittent occlusion of small blood vessels. Patients can be in relative good health "steady state" which may be punctuated by acute exacerbations called "crisis" believed to be precipitated by factors that may affect their haematological indices. *Methods:* This prospective study involved 100 subjects consecutively recruited from haematology day care clinics of the University of Maiduguri Teaching Hospital. This comprised 50 sickle cell anaemia patients (HbS HbS) in vaso-occlusive crisis and 50 sickle cell anaemia patients (HbS HbS) in steady state. EDTA anticoagulated blood samples were collected from all subjects for the determination of packed cell volume, white blood cell counts, platelet counts and differential leukocyte counts using standard methods. *Results:* The mean age ± standard deviations of the subjects in steady state and in vaso-occlusive crisis are 23.94±7.14 and 23.60±6.28. The packed cell volume of patients in steady state and those in crisis are 0.18±0.05 and 0.17±0.04, respectively (p =0.58); the white blood counts of patients in steady state and those in crisis are 14.21±4.27 and 14.56±4.77, respectively (p-value 0.70) and the platelet counts of patients in steady state and those in crisis are 121.44±3.61 and 110.14±3.81, respectively with (p =0.21). The differential leukocyte counts of patients in steady state versus those in crisis are neutrophils. There is no significant statistical difference (p>0.05) in the mean values of PCV, WBC count, Platelet count and differential white cell count between sickle cell patients in steady state and during vaso-occlusive crisis. *Conclusion:* Findings from this study showed that there is no difference in the haematological parameters of sickle cell anaemic patients in crisis state from those in stable state. However, detailed red cell indices could provide baseline

data that would be used in effective evidenced-based management of sickle cell diseases.

## 1. Introduction

Sickle cell disease is a well characterized single amino acid molecular disorder of haemoglobin leading to its pathological polymerization, with resultant red cell rigidity causing poor microvascular blood flow with consequent tissue ischaemia and Infarction [1]. The sickle cell disease is a disorder that results from inheritance of two abnormal allelemorphic genes of the β chains of haemoglobin, at least one of which is the sickle gene; in which sickling of red blood cells produces prominent clinical manifestations [2]. The sickle cell anaemia is a term exclusively reserved for sickle cell disorder as a result of inheritance of homozygous HbS gene. Red cell sickling, a sin qua non of sickle cell disease, is caused by polymerization of hemoglobin tetramer as a result of replacement of glutamic acid by valine at position 6 of β-globin due to mutant sickle gene. Deoxygenation of HbS is crucial in causing conformational change that exposes a hydrophobic patch on the surface of β-globin chain at position 6 of the β-globin. Binding on this site to a complementary hydrophobic site on a β-sub-unit of another haemoglobin initiates polymerization of the haemoglobin tetramer and thus sickling of red cell containing the hemoglobin [3].

The World Health Organization estimated that about 5% of world's seven billion people carry the aberrant haemoglobin gene with more than 200,000 babies born with sickle cell anaemia in Africa alone [4]. The global burden of sickle cell anaemia (SCA) is expected to rise as a consequence of population migration from high prevalent countries to low prevalent countries[5]. Many warnings regarding the effect of epidemiological and demographic transitions in low-income countries and their consequences for SCA burden have been published [5]. In Nigeria, sickle cell disease is among the ten priority non-communicable diseases (NCDs) and it contributes significantly to both child and adult morbidity and mortality. More worrisome was the report that Nigeria by virtue of its population has 40 million people carrying the SCA gene, making it stands out as the most sickle cell endemic country in Africa with an annual infant death of 100,000 representing 8% of infant mortality in the country [6]. There are variations in the incidence of SCA within the country with probably a higher incidence in the northern region due to the absence or suboptimal genetic counseling and awareness programmes.

The severity in the clinical course of sickle cell disease is influenced by variety of intracellular and extracellular factors. Many studies have reported the amount of sickle haemoglobin in the red cells, interaction with other haemoglobins variants and thalassaemia (intracellular factors) and deoxygenation (reduced oxygen tension), infections, exposure to extreme weather conditions, dehydration, and emotional stress (extracellular factors) to be major determinants of clinical course of sickle cell diseases [7], [8], [9]. The clinical course of SCA is typically characterized by variable period of steady state that is periodically punctuated by vaso-occlusive crisis [10]. Sickle cell anaemia runs a variable clinical course ranging from mild disease diagnosed accidentally to severe crippling disease. Patients can be in relative good health termed "steady state" which may be periodically punctuated by acute exacerbations called "crises" which could have sudden onset and eventual fatal outcomes [11].

Crisis is the hallmark of sickle cell anaemia. Although red cell sickling is more prominent during crisis, continuous sickling occurs at lower rate in steady state. For index study, the steady state could be defined as a period free of crisis extending from at least three weeks since the last clinical event and three months or more since the last blood transfusion to at least one week before the start of a new clinical event [11]. The crises are traditionally classified as vaso-occlusive, aplastic, sequestration and hyperhaemolytic crises [12], [13]. Vaso-occlusive crisis (VOC) is preceded by a prodromal experience and if uncomplicated is self-limiting [11]. Aplastic or hypoplastic, sequestration and hyperhaemolytic crises are natively referred to as acute anaemic crises, since they worsen the clinical state.

Due to alarming rate of child mortality and financial burden associated with sickle cell disease (SCD), various studies have been fascinated, some of which have highlighted differences in the haematological profile of individuals with SCA and those without SCA. The variability in the haematological profile in individuals with SCA has also been studied. Several factors known to precipitate the vaso-occlusive crisis include infections, exposure to extreme weather conditions, dehydration, and emotional stress.

SCD patients vary significantly from those of normal HbAA individuals, these patients are able to adapt to their steady state haematological values and remain apparently healthy. The importance of some of the steady state haematological values such as hemoglobin concentration, white blood cell (WBC) and platelet counts in prediction of clinical severity as well as management of SCD has been documented [12]. Lower steady state haemoglobin is associated with higher risk of stroke [13], whereas higher values are reported to have higher rates of severe pain [14]. Furthermore, red cell transfusions beyond the steady state Hb may increase blood viscosity with attendant consequences such as worsening of vaso-occlusion and osteonecrosis. High WBC count (≥ 11 x 109 /L) is associated with SCD complications including cerebrovascular accidents [12], [15]. Other parameters for assessment include the red cell indices which are useful in detecting co-existing causes of anaemia in the patients [16]. In the past two decades, several modalities of treatment of SCD such as blood transfusion and haematinic have been used and these modify the haematological indices of SCD patients. Knowledge of the steady state haematological values of SCD patients is very important for their healthcare providers. Hence, this study sought to evaluate haematological parameters which could be associated with sickle cell anaemia patients during crisis and

compare with other SCD patients in steady state.

## 2. Materials and Methods

### 2.1. Study Area

This prospective study was conducted at the haematology department of the University of Maiduguri Teaching Hospital (UMTH), Maiduguri, Nigeria. UMTH is a major referral medical centre in the North eastern Nigeria, with 500 bed size and sub-specialties in medicine and training of other health care professionals. Maiduguri is the capital of Borno state, which lies on latitude 115$^{o}$N and longitude 135$^{o}$E, and occupies an area of 50,778 square kilo meters. Borno State is bordered by the republic of Niger to the North, Chad to the North –East and Cameroun to the East. The climate of Maiduguri has a mean annual maximum temperature of 35$^{o}$C. The estimated population of Borno state according to 2006 population census report is 4,098,391.

### 2.2. Study Subjects

A total number of 100 subjects were recruited for the study, which comprises 50 sickle cell anaemia patients (HbSS) in vaso-occlusive crisis and 50 sickle cell anaemia patients (HbSS) in steady state. Criteria of inclusion in the study were that the patients were first of all confirmed to have sickle cell anaemia and 50 were in crisis while the other 50 were in steady state.

### 2.3. Sample Collection

5 ml of venous blood was aseptically collected from individual patients with a sterile syringe attached to blood collection plunger and dispensed into vacutainer container containing 1.5mg of Ethylene Di-amine-tetra-acetic acid (EDTA). The blood sample was mixed gently, labeled appropriately and kept for analysis.

### 2.4. Analytical Procedures

Packed cell volume, total leukocyte count, total platelet count and differential leukocyte count (peripheral blood count) were conducted using microhaematocrit centrifuge; Turk's solution and New Improved Neubauer ruled Counting Chamber; Ammonium oxalate solution and New Improved Neubauer ruled Counting Chamber; and Leishman's stained thin film respectively.

### 2.5. Statistical Analysis

The data generated from this study was analysed using the statistical package for social sciences (SPSS) for windows software version (16.0), IBM California Inc. USA. The mean, standard deviation and proportion were determined as applicable. The differences between mean was determined using student t test. P-values less than 0.05 were considered statistically significant.

### 2.6. Ethical Consideration

This study was conducted in accordance with the Declaration of Helsinki, and the protocol was approved by the ethical research committee of the University of Maiduguri Teaching Hospital, Nigeria.

### 2.7. Informed Consent

All subjects gave written and/ or verbal informed consent for inclusion before they voluntarily participated in the study.

## 3. Results

A total of 100 sickle cell anaemia patients were prospectively enrolled in this study. Fifty sickle cell anaemia patients were in crisis while another 50 sickle cell anaemia patients were in steady state. Haematology parameters tests conducted included packed cell volume, total leukocyte count, total platelet count and differential leukocyte count. The mean age ± standard deviation of the subjects in steady state and in vaso-occlusive crisis are 23.94±7.14 and 23.60±6.28, respectively (Table 1). The packed cell volume of patients in steady state and those in crisis are 0.18±0.05 and 0.17±0.04, respectively (p= 0.58) (Table 2). The white blood counts of patients in steady state and those in crisis are 14.21±4.27 and 14.56±4.77, respectively (p= 0.70) and the platelet counts of patients in steady state and those in crisis are 121.44±3.61 and 110.14±3.81, respectively (p=0.21). The differential leukocyte counts of patients in steady state versus those in crisis are neutrophils (%) 66.38±11.64 and 67.78±12.08 (p=0.557), Eosinophils (%) 2.30±3.23 and 2.14±3.12 (p=0.801), Basophils (%) 0.004±0.19 and 0.20±0.14 (p-=0.562), Lymphocyte (%) 31.08±9.69 and 29.44±11.49 (p=0.442) and Monocytes (%) 0.28±0.81 and 0.58±1.18 (p=0.142) (Table 3).

***Table 1.*** *Description of study population based on ages at the time of first receipt of blood transfusion and during the study.*

| Parameters | Steady state (n=50) Mean ± SD | VOC (n=50) Mean ± SD | p-value |
|---|---|---|---|
| Age (years) | 23.94±7.14 | 23.60±6.28 | 0.801 |
| Age at first transfusion (years) | 20.70±1.52 | 18.00±2.32 | 0.347 |

P-value <0.05 is considered significant.
Key: SD= Standard deviation
VOC= vaso-occlusive crisis

***Table 2.*** *Haematological indices of patients in steady state versus those in crisis.*

| Parameters | Steady State (n=50) Mean ± SD | VOC (n=50) Mean ± SD | p-value |
|---|---|---|---|
| PCV (L/L) | 0.18±0.05 | 0.17±0.04 | 0.58 |
| WBC×10$^{9}$/L | 14.21±4.27 | 14.56±4.77 | 0.70 |
| PLT×10$^{9}$/L | 121.44±3.61 | 110.14±3.81 | 0.21 |

P <0.05 is considered significant
Key: SD= Standard deviation
VOC= Vaso-occlusive crisis
PCV= Packed cell volume
WBC= White blood cell
PLT= Platelet.

***Table 3.*** *Differential leukocyte counts of the sickle cell patients in steady state and in crisis.*

| Parameters | Steady State (n=50) Mean ± SD | VOC (n=50) Mean ± SD | p-value |
|---|---|---|---|
| Neutrophils (%) | 66.38±11.64 | 67.78±12.08 | 0.557 |
| Eosinophils (%) | 2.30±3.23 | 2.14±3.12 | 0.801 |
| Basophils (%) | 0.004±0.19 | 0.20±0.14 | 0.562 |
| Lymphocytes (%) | 31.08±9.69 | 29.44±11.49 | 0.442 |
| Monocytes (%) | 0.28±0.81 | 0.58±1.18 | 0.142 |

P-value < 0.05 is considered significant.
Key: SD= Standard deviation
VOC= Vaso-occlusive crisis.

## 4. Discussion

Complex interactions involving sickled red cells, leukocytes, thrombocytes and endothelial cells can lead to vaso-occlusive crises, recurring episodes of ischaemia-perfusion injury and chronic haemolysis. Many different proteins in sickle erythrocytes, endothelial cells, leucocytes and in the fluid phase of blood have been reported to have the potential to modulate the vaso-occlusive process [7]. This study was therefore conducted to evaluate the effects of these precipitated interactions on the haematological indices of patients with sickle cell anaemia in vaso-occlusive crisis.

The mean ages of the subjects in steady state and in vaso-occlusive crisis are 23.94 years (SD±7.14) and 23.60 years (SD±6.28), respectively. This is in conformity with work by Omoti [8] in which the peak incidence was in third decade of life of the subjects.

Continual red cell haemolysis is the hallmark of SCA that is responsible for shortened rate of red cell survival and anaemia [17]. Patients with SCA are known to have higher mean total white blood cell and differentials than non-SCA subjects. Sickle cell anaemia has also been associated with raised mean platelet counts and platelet hyperactivation. Our study found no significant statistical difference between the mean packed cell volume (PCV), mean total white cell counts (WBC) and mean platelet count of sickle cell patients in vaso-occlusive crisis and those of sickle cell patients in steady state. This is consistent with previous studies [8], [18]. This may be so, as vaso-occlusive crisis in SCA are be precipitated by many factors which may not have direct effects on parameters we investigated. There are a melanche of factors (intrinsic and extrinsic) that can cause variability in clinical manifestations of sickle cell anaemia.

The SCD patients usually experience chronic haemolysis, low erythropoietin response and shortened red cell survival which explains the low PCV observed in the SCD subjects of this study [18]. The mean PCV for of the SCD patients corresponded with that reported by Omoti [8], in a work whose subjects were predominantly adults (mean age of 23.7 years). However, it has been reported that SCD patients with lower steady state PCV may have higher risk of SCD-associated complications, especially stroke [13]. The findings of low PCV in vaso-occlusive state SCD group were similar with other studies [8], [20]; although the differences were not statistically significant when compared to those in steady state. The mean PCV values in the SCD patients were lower than reported by Abbas [21]. These observations may reflect possible iron deficiency among the SCD patients in this study area.

Platelets have been largely reported to play crucial roles in the pathogenesis of VOC in SCD, mainly through its interaction with endothelial cells, along with white cells and sickled red cells [22]. Some studies have reported platelet count as a predictor of clinical outcome in SCD [23].

The mean platelet count of the VOC SCD patients was lower than that of SCD patients in steady state. This could be due to the decrease or absent splenic sequestration of platelets in SCA patients in steady state [16]. These findings are in consonance with several other reports [8], [20], [21].

The WBC counts for the SCD patients in this study were comparable to the findings in a previous study in Sudan [18]. The higher values of WBC and Neutrophil counts for the SCD could be due to persistent low grade inflammation and a shift of granulocytes from the circulating compartment [20]. The observation of a higher mean WBC and Neutrophil counts may require further investigation to ascertain if it is due to subclinical infection since SCD patients are known to have higher risk of contracting bacterial infections [21].

## 5. Conclusion

Findings from this study showed that there is no difference in the haematological parameters of sickle cell anaemic patients in vaso-occusive state from those in stable state. However, detailed red cell indices could provide baseline data that would be used in effective evidenced-based management of sickle cell diseases.

## Acknowledgements

We are grateful to staff of haematology department, University of Maiduguri Teaching Hospital, Nigeria for their technical input in this study.

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