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# Haemorrheologic and Fibrinolytic Activities of HbSS, HbAS and HbAA Subjects in Abuja, Nigeria

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Three quarters of sickle-cell cases occur in Africa. A recent WHO report estimated that around 2% of newborns in Nigeria were affected by sickle cell anaemia, giving a total of 150,000 affected children born every year in Nigeria alone. The carrier frequency ranges between 10 and 40% across equatorial Africa, decreasing to 12% on the North African coast and <1% in South Africa. Our aim was to determine the haemorrheologic and fibrinolytic activities of HbSS, HbAS and HbAA subjects in a view to provide information on the status of the activities for proper management. One hundred and seventy (170) subjects were used for this study; 50 were sickle cell (HbSS) patients, 60 were hemoglobin S carriers (HbAS) and the remaining 60 were normal haemoglobin (HbAA) individuals (control group) seen within a six-month period in Abuja, Nigeria had their blood samples analyzed. Haemoglobin electrophoresis, euglobulin lysis time, fibrinogen level, plasma viscosity, haemoglobin and platelet count were determined using standard methods. The mean age (years) of subjects studied were 8.23±1.24, 12.7±1.07 and 13.50±1.46 for HbSS, HbAS and HbAA, respectively. RPV, PLT and FIB concentration of HbSS were significantly raised while Hb level were reduced when compared with HbAA and AS subjects ($p<0.05$). However, the mean values for HbAS and AA subjects fell within the reference value. There was no significant difference ($p>0.05$) in the mean values of ELT for HbAA, AS and SS subjects in this study as they all fall within the reference range. The result shows that there were no significant changes in all the parameters studied based on gender. There was a significantly high RPV and fibrinogen in HbSS patients and reduced level of Hb concentration and platelet count when compared to HbAS and HbAA subjects. Therefore it is recommended that regular check-up and that fibrinogen assay and relative blood viscosity should be included as routine tests in the management of sickle cell anaemia patients.

**Key words:** Fibrinolysis, haemorrheology, HbAA, HbAS, HbSS

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## INTRODUCTION

Sickle Cell Anaemia (SCA) is a serious blood disorder that affects haemoglobin (Hb), the protein found in Red Blood Cells (RBCs) which helps carry oxygen throughout the body. It occurs when a person inherits two abnormal genes (one from each parent) that cause their red cells to change shape. Red Blood Cells (RBCs) with normal haemoglobin A (HbA) move easily through the bloodstream, delivering oxygen to all cells of the body. They can easily squeeze through very small blood vessels. The abnormal red blood cells do not move easily through the blood stream particularly the very small blood vessels; thus they may not be able to deliver enough oxygen to the tissues of the body (Embury *et al*., 1994). The abnormal physiochemical properties of the resulting sickle haemoglobin (HbS) are responsible for sickle cell anaemia in the homozygous state (HbSS). This is due to relative rigidity of sickle cells and formation of aggregate cells particularly in the microvasculature, the viscosity of the blood increases, resulting in vascular endothelium, that is facilitated by acute phase proteins and fibrinectin (Hoffbrand *et al*., 2001). The flow of sickle red blood cells are sluggish, they traverse capillaries poorly and tend to obstruct flow, thereby increasing the sickling of other cells and eventually stopping the flow with subsequent thrombosis causing severe pain, swelling and tenderness (infarction crisis). Sickle cells are phagocytosed in large number, reducing their life span considerably with resulting haemolysis (Haslett *et al*., 1999). Sickle cells in human blood: both normal red blood cells and sickle-shaped cells are present. Sickle-cell disease may lead to various acute and chronic complications, several of which have a high mortality rate (Malowany and Butany, 2012). Migration of substantial populations from these high prevalence areas to low prevalence countries in Europe has dramatically increased in recent decades and in some European countries sickle cell disease has now overtaken more familiar genetic conditions such as haemophilia and cystic fibrosis. In 2010 it resulted in about 29,000 deaths globally (Lozano *et al*., 2012). Three quarters of sickle-cell cases occur in Africa. A recent WHO report estimated that around 2% of newborns in Nigeria were affected by sickle cell anaemia, giving a total of 150,000 affected children born every year in Nigeria alone. The carrier frequency ranges between 10 and 40% across equatorial Africa, decreasing to 12% on the North African coast and <1% in South Africa (WHO., 2012). Anaemia, painful crisis and other complications are associated with Sickle Cell Anaemia (SCA). The pathogenesis of SCA is centered on the sequence of events that occurs between polymerization of deoxy HbS and vaso-occlusion. Cellular dehydration, inflammatory response and reperfusion injury seem to be important pathophysiological mechanisms (Ballas, 1991). Some changes in SCA include evidence of thrombin generation and depletion of natural anticoagulant (Westerman *et al*., 1999) activation of white blood cells and platelets has also been reported (Kaul and Hebbel, 2000). Franck *et al*. (1985) reported that sickle red blood cells stimulate prothrombinase activity. Significant activation of coagulation with consequent increase in fibrinolysis occurs during both sickle cell crisis and in steady state. Semple *et al*. (1994) reported the need for the use of antiplatelet and anticoagulant agents to decrease the incidence of severity of microvascular occlusion in sickle cell anaemia. Viscosity of blood reflects its rheological properties which can be influenced by packed cell volume, plasma viscosity, red cell aggregation and deformability. In Indian, Nilesh *et al*. (2014) obtained high MPV and PDW in HbSS patients as compared to controls; they propose a hypothesis that larger platelets in HbSS patients may predispose them to vaso-occlusive crisis and fibrinogen levels showed a higher increase in crisis, its estimation can be used as a parameter to monitor progression of sickle cell crisis. Akinbami *et al*. (2012) also reported recently that homozygous sickle cell disease patients have lower values of haemoglobin concentration, packed cell volume, red cell indices but higher values of white cell count and platelets compared to haemoglobin a phenotype AA control which was carried out in Lagos, Nigeria. Plasma viscosity depends on the concentration of plasma proteins especially fibrinogen (Dacie and Lewis, 2002). The aim of this research is to evaluate the haemorheologic and fibrinolytic activities of sickle cell anaemia patients with a view to provide more information on their status.

## MATERIALS AND METHODS

A total of 170 subjects residing in Abuja metropolis were considered in the present study within a six-month period. To fulfill the ethical guidelines for human research, permission was obtained from the Ministry of Health, Abuja before recruiting subjects and consent from each subject was also sought and obtained. The hospital is located in the centre of the federal capital territory and both cases and controls included in the study were residents of surrounding districts around the hospital. All confirmed patients of sickle cell haemoglobinopathy diagnosed by the presence of hemoglobin 'S' band and control groups diagnosed by the presence of haemoglobin 'A' on hemoglobin electrophoresis (performed on cellulose acetate strip at alkaline pH 8.6) constituted our subjects. They were further subdivided into three groups: Sickle cell trait (patients whose electrophoresis showed presence of both haemoglobin 'A' band and haemoglobin 'S' band-HbAS genotype), Homozygous Sickle cell disease patients (patients whose electrophoresis showed presence of haemoglobin 'S' band with or without haemoglobin 'F' band-HbSS genotype) and control group (subjects whose electrophoresis showed presence of only haemoglobin 'A'-HbAA).

Out of the 170 subjects, 50 were sickle cell (HbSS) patients attending the Federal Staff Hospital, Jabi, Gwarinpa,

60 were hemoglobin S carriers (HbAS) and the remaining 60 were normal haemoglobin (HbAA) individuals (control group). The sickle cell carriers were included in the study as second control to check the effect of all the parameters studied. The 3 groups comprised male and female subjects with age range 3-36 years. These controls were randomly selected from patients referred for haemoglobin electrophoresis to haematology laboratory and whose haemoglobin electrophoresis pattern was AA type. Patients from which sufficient amount of blood could not be collected for coagulation analysis or whose consent was not obtained were excluded from being controls. Five milliliters of blood was collected from each subject and distributed as follows; 2.5 mL of citrated blood was spun at 2,500 rpm for 10 min to get plasma for fibrinogen (FIB) concentration and Euglobulin Lysis Time (ELT) while 2.5 mL of sequestrated blood was used for haemoglobin estimation, platelet (PLT) count and Relative Plasma Viscosity (RPV). Acetate cellulose electrophoresis method at pH 8.6 was performed to confirm the haemoglobin types of subjects. Euglobulin lysis time was carried out according to the method of Haugie (1986), fibrinogen assay was based on the method of Clauss (1957) purchased from BAUR company (USA). Plasma viscosity was by Reid and Ugwu (1987) method, while haemoglobin and platelet count was determined using Abacus Junior Haematology Analyzer.

**Statistical analysis:** The SPSS version 16.0 was used to analyze data obtained in this study. One way analysis of variance (ANOVA) and student t-test were used to compare the means±SD for Hb, RPV, PLT, FIB and ELT of SCA patients with values of control subjects (HbAA) and sickle cell carriers (HbAS). The p = 0.05 was set as the accepted significance level.

## RESULTS

Table 1 shows the mean age (years) of subjects studied and these were 8.23±1.24, 12.7±1.07 and 13.50±1.46 for HbSS, HbAS and HbAA, respectively. It also shows the mean age of the male and female subjects which were (8.29±1.29, 12.95±1.02 and 14.55±1.07 for HbSS, HbAS and HbAA) and (8.17±1.77, 12.43±1.06 and 12.52±1.09 for HbSS, HbAS and HbAA), respectively. Mean values for haemoglobin, RPV, PLT, FIB and ELT of SCA patients and control subjects is presented in Table 2. The RPV, PLT and FIB concentration of Hb SS were significantly raised when compared with HbAA and AS subjects ($p<0.05$). However, the mean values for HbAS and AA subjects fell within the reference value. The Hb level of HbSS subjects was significantly reduced ($p<0.05$) when compared with that of HbAS and AA which was found to be within the reference range. There was no significant difference ($p>0.05$) in the mean values of ELT for HbAA, AS and SS subjects in this study as they all fall within the reference range (Table 2). Table 3 presents the Hb, RPV, PLT, FIB and ELT levels of SCA subjects based on age. There was no significant change in all the parameters studied though numerically it does appear that the female subjects had raised

Table 1: Demographic characteristics of subjects based on age, gender and Hb types

| Hb type | HbSS | HbSS in steady state | HbSS in crisis state | HbAS | HbAA |
|---|---|---|---|---|---|
| Age (years) | 8.23±1.24 (n = 50) | 8.37±1.22 (n = 40) | 7.68±1.18 (n = 10) | 12.70±1.07 (n = 60) | 13.50±1.46 (n = 60) |
| Males (mean age in years) N = 109 | 8.29±1.23 (n = 26) | 8.49±1.26 (n = 19) | 7.73±1.14 (n = 7) | 12.95±1.02 (n = 28) | 14.55±0.96 (n = 29) |
| Females (mean age in years) N = 121 | 8.17±1.77 (n = 24) | 8.25±1.21 (n = 21) | 7.57±0.55 (n = 13) | 12.43±1.06 (n = 32) | 12.52±1.09 (n = 31) |

Values are Mean±SEM

Table 2: Haemoglobin level, relative plasma viscosity, platelet count, fibrinogen and euglobulin lysis time of SCA patients (HbSS) and control subjects (HbAA and HbAS)

| | Parameters | | | | |
|---|---|---|---|---|---|
| Hb types | Hb (g $L^{-1}$) (125-145) | RPV (cp) (1.47-1.86) | PLT×$10^9$ $L^{-1}$ (150-400) | FIB (g $L^{-1}$) (1.5-4.0) | ELT (min) (90-240) |
| HbAA (n = 60) | 135±0.19 | 1.8±0.04 | 227±6.20 | 4.42±0.25 | 220±11.8 |
| HbAS (n = 60) | 127±0.14[a] | 1.69±0.04 | 213±7.09 | 3.52±0.17 | 204±10.1 |
| HbSS (n = 50) | 84±0.17* | 2.03±0.09 | 304±25.5 | 5.75±0.22 | 205±12.93 |
| F. Calculated | 265.17 | 8.07 | \=]11.14\[ | 25.92 | 0.63 |
| F. Critical | 3.05 | 3.05 | 3.05 | 3.05 | 3.05 |
| p-value | p<0.05 | p<0.05 | p<0.05 | p<0.05 | p>0.05 |

Values are expressed as means±SEM, *Significantly different from HbAA, [a]Significantly different from HbAS

Table 3: HB, RPV, PLT, FIB and ELT levels of SCA subjects based on gender (mean±SD)

| Parameters | Males (n = 26) | Females (n = 24) | T. cal. | T. tab. | p-value |
|---|---|---|---|---|---|
| Hb (g $dL^{-1}$) | 83.0±0.26 | 84.0±0.26 | 0.15 | 2.01 | $p>0.05^{NS}$ |
| RPV (cp) | 2.0±0.08 | 2.1±0.17 | 0.32 | 2.01 | $p>0.05^{NS}$ |
| PLT (×$10^9$ $L^{-1}$) | 272.0±26.0 | 361.0±47.6 | 1.65 | 2.01 | $p>0.05^{NS}$ |
| FIB (g $L^{-1}$) | 6.0±0.27 | 5.6±0.31 | 1.13 | 2.01 | $p>0.05^{NS}$ |
| ELT (min) | 206.0±19.7 | 205.0±17.2 | 0.05 | 2.01 | $p>0.05^{NS}$ |

NS: No significant difference

Table 4: HB, RPV, PLT, FIB and ELT of SCA subjects based on age

| | Parameters | | | | | |
|---|---|---|---|---|---|---|
| Age (years) | 0-10 (n = 15) | 11-20 (n = 20) | 20≥ (n = 15) | Calculated F | Critical F | p-value |
| Hb (g $L^{-1}$) | 85.0±0.31 | 81.0±0.33 | 85.0±0.31 | 0.56 | 3.19 | $p>0.05^{NS}$ |
| RPV | 2.2±0.28 | 2.0±0.09 | 1.9±0.09 | 0.01 | 3.19 | $p>0.05^{NS}$ |
| PLT ($\times10^9$ $L^{-1}$) | 318.0±55.9 | 313.0±49.0 | 320.0±57.4 | 0.73 | 3.19 | $p>0.05^{NS}$ |
| FIB (g $dL^{-1}$) | 5.9±0.39 | 5.7±0.33 | 5.9±0.38 | 0.15 | 3.19 | $p>0.05^{NS}$ |
| ELT (min) | 212.0±24.5 | 203.0±22.4 | 203.0±21.0 | 0.05 | 3.19 | $p>0.05^{NS}$ |

Values are Mean±SD, NS: No significant difference

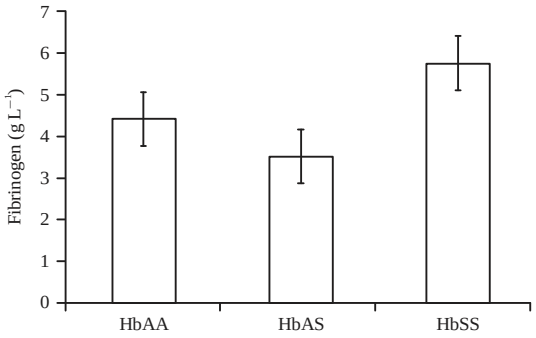


Fig. 1: Median fibrinogen concentration of HbAA (Control group), HbAS (Sickle cell triat) and HbSS (Sickle cell anaemia patients)

Hb, RPV and platelet count when compared with their male counterpart while FIB and ELT appeared to be similar. The Hb, RPV, PLT, FIB and ELT values of SCA subjects based on gender is shown in Table 4. The result shows that there were no significant changes in all the parameters studied with reference to gender. Figure 1 shows fibrinogen level of HbAA (control group), HbAS (sickle cell trait) and HbSS (sickle cell anaemia) subjects. The mean fibrinogen concentration level was 4.42±0.25, 3.52±0.17 and 5.75±0.22 g $L^{-1}$ for HbAA (n = 60), HbAS (n = 60) and HbSS (n = 50) respectively. It shows that HbSS had fibrinogen concentration level that was significantly higher than the levels in the HbAA and HbAS ($p<0.05$).

## DISCUSSION

This study highlights changes in the haemorheologic and fibrinolytic activities of sickle cell anaemia patients when compared to sickle cell trait carriers and normal haemoglobin phenotype AA. The haemorheologic activities in Sickle Cell Anaemia (SCA) observed in this study shows increased relative plasma viscosity and platelet counts as well as a decrease in haemoglobin concentration. These results are in agreement with those of Kaul *et al*. (1983), Awodu and Famodu (2007) and Akinyoola *et al*. (2009). The reduced level of Hb was expected considering the degree of chronic haemolysis, which occurs in sickle cell anaemia patients and the adaptation of the patients to low haemoglobin levels. Furthermore there is also a blunted response to erythropoietin secretion in SCA patients and the rate of increase is not proportional to the degree of anaemia. This may be due to a right-shift of the haemoglobin dissociation curve seen in sickle cell anaemia disease as reported by Morris *et al*. (1991). The present study shows that there is increase in relative plasma viscosity in sickle cell anaemia compared with the sickle cell carriers (HbAS) and normal control subjects (HbAA). This is in agreement with Aluoch (1998) report who stated that the sickling of erythrocytes increases viscosity and reduces the rate of both local circulation and arterio-venous transit time. This causes occlusion of capillaries by micro-thrombin. Chien (1977) reported that the viscosity of oxygenated blood from patients with sickle cell anaemia (HbSS) was found to be abnormally increased. Relative plasma viscosity and fibrinogen level in sickle cell anaemia subjects was observed to be increased in HbSS subjects when compared with HbAS and normal control (HbAA) subjects. Our findings of significantly elevated concentration of fibrinogen among HbSS patients as compared to HbAS and HbAA (control subjects) has been described by other authors (Famodu and Reid, 1987; Buseri *et al*., 2007; Nilesh *et al*., 2014). Most researchers have linked the hypercoagulable state in HbSS patients to increased levels of fibrinogen concentration (Famodu and Reid, 1987; Nsiri *et al*., 1996; Ataga and Orringer, 2003). Recent studies by Ajayi *et al*. (2007), Emojevwe and Igweh (2012), Ekwere *et al*. (2013) and Johnkennedy *et al*. (2013) in some other parts of Nigeria reported higher fibrinogen concentration in HbSS than in HbAA and HbAS. The values were higher than the values reported from our locality. This could be due to the different methods used by the authors in carrying out the test. Nevertheless, the basic fibrinogen physiological function in hemostasis is the development of a fibrin network; it is also a major determinant of whole blood viscosity (Chien *et al*., 1967). This effect on viscosity is more pronounced at low shear rates as is the microvasculature in sickle cell crisis and hence it has been proposed that raised fibrinogen concentration may be a contributory factor to red cell slugging seen during crisis (Gordon *et al*., 1974). Although some researchers do not consider the raised fibrinogen concentration to be specific (Famodu and Reid, 1987) since fibrinogen is an acute phase reactant, which degree may rise in any condition that causes inflammation or tissue damage. Buseri *et al*. (2007) suggested that the raised fibrinogen level observed in HbSS patients may be due to increased production, as a reactive process probably in response to the chronic hemolytic process (Famodu and Reid, 1987). From the study, Euglobulin Lysis

Time (ELT) showed similar values both in HbSS and HBAS as well as in normal control subjects (HbAA) which appeared to fall within the normal range (90-240 min) but with lower values in HbSS and HbAS when compared with control subjects (HbAA). Again, Aluoch (1998) and Famodu *et al*. (1990) reported increase in ELT in SCA when compared with normal control HbAA which is contrary to our findings (Table 1), but in agreement with ta study by Akinyoola *et al*. (2009). The differences may be due to the methods used for the assay. The ELT is a sensitive measure of fibrinolytic activity. However, this method is not as specific as benchmark tests like D-Dimers and assay of protein C and protein S activities. Sickle cell anaemia (HbSS) subjects had higher platelet counts compared with normal control (HbAA) subjects and sickle cell carrier (HbAS) subjects. The Hb levels of HbSS where lower when compared with control (HbAA) and carriers (HbAS). This could be due to the degree of chronic haemolysis. The possible changes in the haemorheologic and fibrinolytic activities of sickle cell anaemia subjects were investigated in this study. Some level of changes in the parameters studied has been observed in SCA subjects. The knowledge of these changes will be necessary in the management of sickle cell anaemia conditions.

## CONCLUSION

There was a significantly high RPV, fibrinogen and ELT in HbSS patients and reduced level of Hb concentration and platelet count when compared to HbAS and HbAA subjects. Hyperfibrinogenaemia and increase in blood viscosity in sickle cell anaemia could lead to blood stasis and thrombosis in the blood vessels. Conversely, there were no significant differences in all the parameters studied among the age groups and between the males and females, so gender and age do not affect these parameters. The findings of this study suggest education about caring and regular check-up for individuals with sickle cell anaemia in order to maintain a steady state. We therefore recommend that complete blood count, fibrinogen assay, relative blood viscosity and euglobulin lysis time tests should be included as routine tests in the management of sickle cell anaemia patients.

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