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**Original Research Article**

# Transcranial Doppler imaging ultrasound assessment of cerebral blood flow velocity and abnormalities in steady-state sickle cell anaemia children, Southwest Nigeria

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## ABSTRACT

**Background:** Monitoring cerebral blood flow velocity in children with sickle cell anaemia is valuable and advocated and early detection of abnormal velocity affords appropriate management. This study assessed the blood flow velocities in the large intracranial arteries of the participants and determined abnormalities (risks for stroke).
**Methods:** The blood flow velocity in the middle and anterior cerebral arteries of the study participants (2–14 years) was assessed using a transcranial doppler (TCD) imaging ultrasound machine. The risk of stroke for each patient was determined by the greatest time-average mean maximum velocity (TAMMV) in centimeters/second (cm/s) in any of the insonated arteries. And using the Stroke Prevention Trial (STOP) criteria, the subjects were classified into having standard, conditional or high risk for stroke.
**Results:** Out of the 110 participants, males were 61 (55.5%) and females 49 (44.5%). The overall mean TAMMV was 135.50±28.62 cm/s and the 2–5-year-old group presented the highest mean TAMMV (141.31±29.97). The overall mean TAMMVs for the middle and anterior cerebral arteries were 151.95±39.29 cm/s and 117.38±39.85 cm/s, respectively ($t=8.583$, $p<0.001$). According to the STOP criteria, fifty-four (49.1%), 40 (36.4%) and 16 (14.5%) of the subjects had standard, conditional and high risk for stroke, respectively. A comparison of the pattern of risk for stroke identified by Stop criteria (non-imaging) and the adjusted Stop criteria (imaging) revealed a statistically significant difference ($p<0.001$).
**Conclusions:** The prevalence (50.9%) of abnormal velocity (Stop criteria) in this study was high and therefore, regular measurement of the TAMMV in SCA patients is recommended.

**Keywords:** Abnormalities, Children, Cerebral blood flow, Sickle cell anaemia, Velocity

## INTRODUCTION

Sickle cell anaemia (SCA) is one of the most common genetic hematologic diseases in the world and Nigeria has the largest burden, with a prevalence of 3%.[1-5] SCA patients suffer many complications but stroke is one of the most feared causes of morbidity and mortality.[5] The World Health Organization estimates that 70% of SCA deaths in Africa are preventable with simple, cost-effective interventions.[4] TCD ultrasound is a noninvasive method used to measure blood flow velocity in the intracranial arteries. Imaging or non-imaging ultrasound machines are commonly used. Imaging provides more accurate identification and visualization of vessels and

their velocities.[6,7] However, the values in imaging TCD have been found to be ~10% lower in stroke risk prediction.[6,8,9] TCD has a sensitivity of 81% and specificity of 91% in detecting stroke risk in SCA children.[7] Additionally, compared with cerebral angiography, it has a sensitivity of 90% and a specificity of 100%.[10]

In accordance to the stroke prevention trial (STOP) criteria, the cut-off for normal cerebral blood flow velocity (standard risk) is <170 cm/s. Values ranging from 170–199 and ≥200 cm/s are referred to as conditional and high risks, respectively.[11] A child with a high risk for stroke has a 40% chance of developing stroke, whereas it has 4−7% and 2% chances with conditional and standard risks, respectively.[12] In SCD, elevated cerebral blood flow velocity >170 cm/s, particularly in the middle cerebral artery (MCA), is a significant predictor of stroke risk.[13] However, in a case series, it was reported that children who previously had low TCD velocities (≤70 cm/s) suffered some form of cerebral insult, which included overt cerebral infarctions, silent stroke or transient Ischaemic attack.[14] Therefore, it is imperative to detect early children with sickle cell disease having abnormal cerebral blood flow velocity, which will allow the healthcare providers and caregivers to plan appropriate treatment modalities to reduce associated morbidity and mortality and improve patients' quality of life.[12,15,16]

Using TCD ultrasound, the prevalence of abnormal cerebral blood flow velocity (abnormal risk of stroke) among SCA children in Nigeria ranged between 4.7% and 10.8%.[10,12,16-18] To the best of the authors' knowledge, all these previous cerebral blood flow studies among SCA children in Nigeria used nonimaging TCD technique.

Therefore, this study aimed to assess the blood flow velocity in the cerebral arteries (middle cerebral artery (MCA) and anterior cerebral artery (ACA)) of SCA patients aged 2−14 years in Osogbo, South-west Nigeria using TCD ultrasound imaging technique and to use the velocity to determine the risk for stroke.

## METHODS

The participants for this study were recruited from the paediatric hematology clinic and TCD ultrasound scan was carried out at the Radiology Department, Osun State University (UniOsun) Teaching Hospital, Osogbo, Nigeria (formerly Ladoke Akintola University of Technology (LAUTECH) Teaching Hospital (LTH), Osogbo Osun State, Nigeria).

The study was cross-sectional and descriptive in design. The study participants, children with steady-state SCA, aged 2–14 years, attending routine paediatric hematology clinics, were recruited through nonprobability sampling methods. Patients who had any crisis within the last 4 weeks before the data collection, who were on chronic blood transfusion, who already had a stroke or suffering from other haemoglobinopathies and whose parents'/guardians' consent or older children's assent could not be obtained were excluded from the study.

The study protocol was approved before data collection by the Research Ethics Committee of LTH, Osogbo, Nigeria, with approval number LTH/EC/2017/04/308. The scope and methods of the study were explained to the potential subjects and parents/guardians and were informed that participation in the study was voluntary and that they could withdraw from the study at any stage without any misgivings or made to give reason(s). Written informed consent and assent were obtained from all the parents/guardians of the subjects and sufficiently old study participants, respectively. Additionally, all ethical principles guiding the conduct of research involving human subjects were strictly adhered to and in accordance with the Declaration of Helsinki 1975, as revised in 2013.

The minimum sample size for this study was calculated using a 6.9% prevalence of abnormal high-risk blood flow velocity recorded by Oniyangi et al among children with SCD.[18] The minimum sample size (n) for this study was determined using the Leslie–Kish formula; $n=z^2pq/d^2$. Where, n=sample size calculated, P is the prevalence at 6.9%, q=1−p, Z=standard deviation at 95% confidence level=1.96, d=level of precision at 5%.[19]

$n = 1.96^{\times 2}\ 0.069\times 0.931/0.05^2 = 98.7$

Therefore, the minimum sample size for this study was 99 steady-state SCA children.

Data were collected between January and July 2018. The date of birth and age were recorded for each subject. Before the TCD imaging ultrasound scan, the procedure was again explained. The following precautionary measures were taken before and during the procedure; each subject was reassured, kept calm, awake and alert.

Each subject was made to lie in a supine position with the head adjusted with a pillow to access the temporal windows. A small quantity of ultrasound gel was applied to the patient's temporal region of the skull, which served as the acoustic window.

The TCD probe was placed on the acoustic window, which allowed direct visualization of the insonated vessels (middle and anterior cerebral arteries of the circle of Willis). A greyscale image (hypo-echoic heart-shaped cerebral peduncles and echogenic star-shaped basilar cistern), the reference landmark for the circle of Willis, was visualized on the screen.

Colour Doppler was activated, which revealed colour-coded blood flow. The middle cerebral artery (MCA) is recognized by its direction of blood flow towards the

transducer. The anterior cerebral artery (ACA) was visualized distal to the bifurcation of the MCA and flowed away from the transducer. The time-average mean maximum velocity (TAMMV) of blood flow in both arteries (the MCA and ACA) was measured and recorded for both sides of the temporal bone. The ultrasound gel was subsequently removed and the patients were removed from the couch. The procedure lasted 30 minutes.

Using transcranial Doppler imaging ultrasound time-average mean maximum velocity (TAMMV), the velocity in each of the arteries (2 MCAs and 2 ACAs) on both sides of the temporal bone was measured in centimeters per second (cm/s). The overall mean TAMMV for each study participant was the mean of the four arteries' TAMMV values. The Stroke Prevention Trial (STOP) criteria were used to assess each subject's risk for stroke using TAMMV values: <170 cm/s; standard risk, 170-199 cm/s; conditional risk and ≥200 cm/s; high risk.[11]

Additionally, an attempt was made to determine the prevalence of various types of risk of stroke using adjusted STOP criteria, as the value of TCD imaging is approximately 10% less than that of STOP criteria (non-imaging) values.[6,8,9] Therefore, the cut-offs for the risk of stroke according to adjusted STOP criteria (TCD imaging values) are as follow: <153 cm/s, standard risk, 153-179.9 cm/s; conditional risk and ≥180cm/s, high risk.[9] The risk of stroke for each of the subjects was determined by the highest TAMMV value in any of the insonated arteries.

All the information obtained was imputed into a personal computer and analysed using the Statistical Package for Social Sciences (SPSS) version 22 (SPSS Chicago Inc; IL, USA). The data are presented in the tables. Continuous variables are expressed as the means (standard deviations), medians and modes. Means were compared via Student's t-test and one-way ANOVA. Comparisons of categorical variables and tests for associations were performed via chi-square (x2) tests. The level of statistical significance was set at o<0.05.

## RESULTS

One hundred ten children with SCA were studied, including 61 (55.5%) males and 49 (44.5%) females. The overall mean age of the children was 7.17±3.77 years, with 7.16±3.77 for males and 7.17±3.81 years for females. Fifty (45.5%), 33 (30%) and 27 (24.5%) of the participants were in the 2−5, 6−10 and 11−14-yeas age groups, respectively.

The overall mean TAMMV was 135.50±28.62 cm/s (range 66.88−223.26). The MCA and ACA overall mean TAMMVs were 152.00±39.28 cm/s and 117.74±39.53 cm/s respectively (t=8.915, p<0.001). The mean TAMMVs for the right and left MCAs were 151.49±41.63 cm/s (range 72.58–291.29) and 152.40±36.95 cm/s (range 52.37–265.36), respectively (t=0.171, p=0.865), whereas the right and left ACA values were 118.95±42.00 cm/s (range 37–223.40) and 115.80±37.69 cm/s (range 47–220.81) respectively (t=0.539, p=0.590).

Table 1 presents the mean overall, the mean MCA and ACA TAMMVs in cm/s in relation to sex and age groups and there was no statistically significant difference in the mean values. On further analysis, however, the overall mean TAMMV of the right MCA and left MCA in the 2−5 years age group is significantly greater than the 11−14 years age group (Right MCA, t=15.30, p<0.001, left MCA, t=2.73, p=0.008). Blood flow velocities could not be determined in one or two arteries of some study participants (left MCA 2, right ACA 6 and left ACA 11) because the ultrasound machine returned no readings for the arteries and were regarded as missing values.

According to the STOP criteria, 54 (49.1%) of the participants had standard (normal) risk, whereas 56 (50.9%) had abnormal cerebral flow velocity: 40 (36.4%) had conditional risk and 16 (14.5%) had high risk. Additionally, 57.4% of the males and 43.0% of the females had abnormal velocities. The prevalence of a high risk for stroke was relatively high in females and those aged 6−10 years, but the differences were not statistically significant. The prevalence rates of various types of risk for stroke in relation to sex and age group are shown in Table 2.

Comparison of the prevalence of risks for stroke determined by the STOP criteria and the adjusted STOP criteria. Considering that the imaging TCD value is approximately 10% lower than non-imaging STOP criteria, the prevalence of risks for stroke was determined via adjusted STOP criteria (TCD imaging values), with standard risk <153 cm/s, conditional risk 153-179.9 cm/s and high risk ≥180 cm/s. The prevalence of the risks for stroke in both classifications were compared and display on Table 3. The prevalence rates of the stroke risks differed significantly (p <0.001).

The comparisons of the cerebral arteries time-average mean maximum velocity between males and females and between various age groups, are shown in Table 1. Apparently, there are no statistically significant differences in the comparisons. Table 2 displays the risks of stroke prevalent among each sex and age group, with no significant differences. High risk for stroke is more prevalent among females and the 6−10 age group. The prevalence of risks for stroke using the 2 criteria (STOP criteria (non-imaging ultrasound) and adjusted STOP criteria (imaging ultrasound) is displayed in table 3. Outcomes show significantly different prevalence of risks of stroke.

**Table 1: Study participants' cerebral arteries time-average mean maximum velocity in cm/s in relation to gender and age group.**

| | TAMMV (cm/sec) | | | | |
|---|---|---|---|---|---|
| | Right MCA Mean±SD (N) | Right ACA‡ Mean±SD (N) | Left MCA‡ Mean±SD (N) | Left ACA‡ Mean±SD (N) | Overall Mean±SD (N) |
| **Gender** | | | | | |
| Male | 151.18±40.70 (61) | 119.39±43.01 (61) | 148.22±36.08 (60) | 116.09±39.33 (56) | 134.01±26.84 (61) |
| Female | 151.88±43.17 (49) | 118.33±41.04 (43) | 157.63±37.72 (48) | 115.42±35.90 (43) | 136.93±30.98 (49) |
| t value | 0.087 | 0.126 | 1.32 | 0.087 | 0.529 |
| P value | 0.9306 | 0.900 | 0.190 | 0.931 | 0.598 |
| **Age group (in years)** | | | | | |
| 2-5 | 156.68±38.12 (50) | 123.10±47.53 (49) | 160.49±29.78 (49) | 121.33±36.11 (46) | 141.31±29.97 (50) |
| 6-10 | 154.09±48.71 (33) | 110.83±29.14 (29) | 150.94±44.65 (32) | 115.53±37.49 (28) | 133.92±26.63 (33) |
| 11-14 | 138.72±37.07 (27) | 120.19±43.25 (26) | 139.46±36.09 (27) | 105.92±40.16 (25) | 125.90±26.33 (27) |
| f value | 1.748 | 0.789 | 2.961 | 1.365 | 2.686 |
| P value | 0.179 | 0.457 | 0.056 | 0.260 | 0.073 |

‡Some columns would not add up to 110 because of missing arteries during ultrasound scan.

**Table 2: Prevalence of various types of risks for stroke in relation gender and age group.**

| Parameters | Risks for stroke N (%) | | | | | |
|---|---|---|---|---|---|---|
| | Standard | Conditional | High | Total | $\chi^2$ | P value |
| **Gender** | | | | | | |
| Male | 26 (42.6) | 27 (44.3) | 8 (13.1) | 61 (100) | 3.71 | 0.157 |
| Female | 28 (57.1) | 13 (26.5) | 8 (16.5) | 49 (100) | | |
| Total | 54 (49.1) | 40 (36.4) | 16 (14.5) | 110 (100) | | |
| **Age group (in years)** | | | | | | |
| 2-5 | 24 (48.0) | 18 (36.0) | 8 (16.0) | 50 (100) | 5.12 | 0.275 |
| 6-10 | 13 (39.4) | 13 (39.4) | 7 (21.2) | 33 (100) | | |
| 11-14 | 17 (63.0) | 9 (33.3) | 1 (3.7) | 27 (100) | | |
| Total | 54 (49.1) | 40 (36.4) | 16 (14.5) | 110 (100) | | |

**Table 3: Pattern of risks for stroke in relation to STOP criteria and adjusted STOP criteria.**

| Risks for stroke | Classification of risks for stroke N (%) | |
|---|---|---|
| | STOP criteria (non-imaging TCD) | Adjusted STOP criteria by 10% less (imaging TCD) |
| **Standard** | 54 (49.1) | 33 (30) |
| **Conditional** | 40 (36.4) | 32 (29.1) |
| **High** | 16 (14.5) | 45 (40.9) |
| **Total** | 110 (100) | 110 (100) |

$\chi^2$ =19.74, Df =2, p<0.001.

## DISCUSSION

In the present study, the overall mean TAMMV was 135.50±28.62 cm/s. This value was lower than the 152±27.0 and 141±35.0 cm/s reported by Lagunju et al in Nigeria and Adams in the African American study respectively.[12,20] The reason for this disparity might be that these 2 studies were longitudinal, unlike the cross-sectional design of the present study. TAMMV values change with multiple TCD examinations.[21] Additionally, the disparity could be because imaging TCD was used in this study, as its values are usually ~10% lower than those of the nonimaging TCD in stroke risk prediction.[6,8,9] The middle cerebral artery (MCA) had significantly greater velocity values than the ACA did in this study, an observation that is consistent with earlier reports and that stroke is likely to occur in the MCA.[12,22-24] Adekile et al reported that among Arab children, the

usual site of stenosis with high TAMMV values was the large arteries of the Circle of Willis, especially the MCA.[25] The overt strokes in these arteries could be due to the large artery vasculopathy affecting the intracranial internal carotid arteries and proximal middle cerebral arteries.[25] The MCA has the largest calibre (approximately 3 mm) among the arteries of the Circle of Willis and, as such, puts it at greater risk for overt stroke. Therefore, the higher TAMMV value in the MCA is not surprising and supports the assertion or prediction that stroke is likely to occur in the artery.[25] In this study, some patients' velocities could not be recorded and zero velocity returned. This occurrence could be secondary to a vascular spasm or occlusion. These children were singled out and the parents were advised to perform magnetic resonance imaging (MRI) to further evaluate the affected participants so that appropriate management could be instituted.

Patients aged 2 to 5 years had the highest mean TAMMV, which was similar to the findings of Lagunju's study.[12] However, some other previous studies reported the highest values among those aged 6–10 years.[16,18,23] Possible explanations for the disparity in the peak age for the highest velocities could be the nonuniformity of the age group classification used and the unequal number of subjects in each age group in the previous studies. This was evident in this study, where those aged 2–5 years accounted for the highest proportion of the study participants and recorded the highest mean TAMMV. This was alluded to by Oniyangi's study, which included the greatest number of studied patients between the ages of 5 and 10 years and reported that the peak age for the highest velocities was the same age group (5–10 years).[18] Additionally, studies have shown that children between the ages of 2 and 5 years are at greater risk of stroke than older children are, but the reason for this difference is still not well understood.[12,26]

In accordance with the STOP criteria, the prevalence of high risk for stroke among the study participants in this study was 14.5%.[11] The observed prevalence is comparable to the 12.3% reported by Adams et al, among 190 African American patients between the ages of 3 and 18 years.[20] A higher prevalence (34%) of high risk for stroke was reported by Riebel et al, among neurologically asymptomatic SCD children and young adults and 27% in the prospective Creteil newborn cohort study.[26,27] However, Lagunju et al reported lower prevalences of 4.6% and 8.2% in cross-sectional and prospective studies, respectively, in Ibadan Nigeria.[12,16] In addition, Oniyangi and Adekunle, both in Nigeria reported lower prevalence rates of 6.9% and 10.8%, respectively, for high risk for stroke among the patients studied.[18,23]

Furthermore, the prevalence rate of high risk for stroke observed in the present study is higher than in earlier studies in Africa may be explained by the different methodologies (instruments) used.[12,16,18,23] While imaging TCD was employed in this study, Lagunju et al and Adekunle employed the use of non-imaging TCD ultrasound machines.[12,23] The non-imaging machine employs the use of sound waves to measure the velocity of cerebral arteries, whereas duplex imaging combines Doppler ultrasound with real-time ultrasound imaging of the arteries to identify cerebral vessels easily and accurately. In addition, these previous Nigerian prevalence studies examined both haemoglobin SS (HbSS) and haemoglobin SC (HbSC) patients together and high-risk velocities were found only in SCA (HbSS) patients. On the other hand, only SCA patients were assessed in the present study.[16,23] The dilution effect of assessing both SCA and HbSC in the same study could be responsible for the lower prevalence observed in these previous studies. SCA patients are known to have worse disease severity than their HbSC counterparts.[28]

Additionally, Creteil's newborn study and Riebel's study also employed the use of imaging TCD and reported an even greater prevalence of a high risk for stroke.[26,27] These two studies were longitudinal prospective cohort studies in which multiple contacts and examinations were performed, contrary to the present study. The time average maximum velocity has been documented to change from conditional to high-risk velocity and vice versa with multiple examinations.[26,27] In addition, Riebel et al, had a smaller sample size of 47 patients and insonated 11 arteries in the circle of Willis than the 4 arteries insonated in this study.[27] The higher prevalence of high risk of stroke in the two studies (Riebel et al and Creteil newborn cohort study) might also be due to multiple contacts and an increased number of insonated arteries.[26,27]

A relatively higher but not significant prevalence of high risk for stroke was observed among the age group of 6–10 years. This finding is consistent with the findings of the Oniyangi and Adekunle studies, which reported a relatively high prevalence of high risk for stroke among patients aged 5–10 years.[18,23] In contrast, Lagunju et al reported that the younger age group was more strongly associated with a high risk for stroke in a correlation study.[16] This occurred despite most of the study participants being older than 5 years. The authors did not provide any definitive explanation for this finding; however, they noted that other indepen6dent and important risk factors for stroke such as anaemia and haemolysis, might be responsible.[16]

The attempt to classify the risks for stroke using the adjusted STOP criteria produced a statistically significant pattern of prevalence of different types of risk for stroke (Table 3). This shows the challenge / dilemma faced when the STOP criteria are used to classify imaging TCD values. There should be concerted efforts to validate imaging TCD values for use.

An imaging TCD machine was used in the present study to assess the velocities of the cerebral arteries of the study participants and the STOP criteria, which are based on

non-imaging TCD values were used primarily to classify the TAMMV values into various types of risk for stroke. The corresponding values of imaging are approximately 10% less than the non-imaging TCD values.[6,8,9] Therefore, some of the patients might have been misclassified. The strengths of this study stemmed from the attempt to classify the risks for stroke using adjusted STOP criteria values. This effort demonstrated the challenge faced by researchers while using non-imaging (STOP criteria) to classify values obtained by a TCD imaging ultrasound machine.

## CONCLUSION

This study revealed that SCA patients are at risk of developing stroke on the basis of the high prevalence of high risk for stroke. The 2–5 years age group had the highest mean TAMMV value, whereas the 6–10 years age group had a higher but nonsignificant prevalence of high risk for stroke. Additionally, strokes are more likely to occur in the MCA than in the ACA because the former has significantly higher velocity values. Therefore, it is imperative to screen SCA patients as early as possible to detect any propensity for strokes and manage it to reduce morbidity and mortality associated with strokes. Additionally, children who have conditional velocities should be followed up with repeated TCD examinations to detect early worsening velocities and institute appropriate stroke prevention measures. TCD imaging values should be validated for use to overcome the dilemma faced by researchers using the STOP criteria to classify values obtained by a TCD imaging ultrasound machine.

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