Short course blood transfusion therapy with hydroxyurea, a functional strategy in the management of stroke in children with sickle cell disease.

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Abstract

Cerebrovascular accidents are serious complications of Sickle Cell Disease (SCD). Children with abnormal transcranial doppler (TCD) readings are at higher risk for stroke, and those with prior strokes have increased risk of recurrence. Chronic blood transfusion therapy is the standard treatment for stroke prevention; hydroxyurea, a recommended alternative, is less effective. This study explores the use of modified short blood transfusion therapy (BTT) combined with hydroxyurea for stroke prevention in SCD.

We reviewed medical records of 170 children (ages 2-16) with abnormal TCD or prior stroke treated with monthly BTT for 6-8 months and hydroxyurea. TCD results and stroke incidence were assessed one year after discontinuing BTT.

Among the children, 136 (80%) had abnormal TCD, 15(11.2%) had current stroke, and 19 (8.8%) had prior stroke. After discontinuation of BTT, abnormal TCD readings decreased significantly to 18.7% and 16.9%, ($p<0.05$); those with normal TCD increased significantly from 38.8% to 52.8%, ($p<0.05$) after 1 year. TCD velocity decreased significantly during the same period ($p<0.05$). Only 2 (1.5%) children with abnormal TCD, experienced stroke. Overall, 13 (7.8%) had stroke by one-year post BTT.

In conclusion, combination of short-course BTT and hydroxyurea significantly reduced stroke risk and incidence of stroke in children with SCD.

Introduction

Sickle cell disease (SCD) is the most common haemoglobinopathy worldwide, especially in sub-Saharan Africa, the Middle East, the Caribbean, India, and parts of the Mediterranean. Africa bears the highest burden, with over two-thirds of the ~305,800 annual global cases, contributing to 50–90% of childhood mortality and millions of lost disability-adjusted life years.[1-5] Sickle cell anaemia (SCA), the most severe form, results from inheriting haemoglobin S (HbS) from both parents. Under low oxygen, HbS polymerises, distorting red blood cells into rigid sickle shapes with reduced deformability. While initially reversible, repeated sickling causes permanent membrane damage and dense, irreversibly sickled cells. These cells, together with activated leukocytes and platelets, adhere to endothelium, driving vaso-occlusion and tissue infarction. Haemolysis releases free haemoglobin, depleting nitric oxide and, along with ischaemia–reperfusion injury, provoking inflammation, endothelial dysfunction, and progressive vasculopathy. This pathophysiology underlies multi-organ complications such as recurrent pain crises, severe cardiopulmonary disease, and increased stroke risk.[1,2,6]

Stroke is one of the most devastating complications of SCD and about 11% of children with SCD would have overt stroke by 16 years of age and 37% develop silent stroke by age 14 years

with associated cognitive impairments.[7,8] Also, children who have had a first stroke are at significant increased risk of recurrence.[9,10] A multicenter study in Nigeria reported an overall stroke prevalence of 12.4 per 1000 patients, with recurrence rate of 23.9% and multiple strokes in 2.97 per 1000; the overall stroke rate in adults was 17.7 per 1000 and 7.4 per 1000 in children. [11] The pathophysiology of ischaemic stroke in SCD is not fully understood, however, the interplay of haemoglobin polymerisation, repeated sickling and endothelial damage most likely contribute to stenosis and subsequent occlusion of large arteries in the brain.[10,12]

Transcranial Doppler (TCD) measurement of cerebral arterial blood flow is a key stroke risk predictor in SCD. Elevated time-averaged mean maximum velocity (TAMMV) in the distal internal carotid, or proximal middle or anterior cerebral arteries, correlates with higher risk. Velocities >200 cm/s indicate an abnormal TCD and confer over 40% stroke risk within three years, while 170–199 cm/s is considered conditional, with an increased likelihood of progressing to abnormal levels.[10,13-14]

The Stroke Prevention Trial in Sickle Cell Anemia (STOP), confirmed transcranial doppler as screening tool for prevention of stroke in SCD by showing that regular blood transfusions, that maintained HbS fractions at below 30% of total haemoglobin, reduced incidence of first stroke by 92%. [15] The STOP2 trial, however, showed that discontinuing transfusions led to reversal to abnormal TCD velocity in 14 participants and two participants had overt stroke within one year of discontinuing blood transfusion therapy (BTT). It was, therefore, recommended that blood transfusions should be continued indefinitely in children with abnormal TCD velocity. [16] Despite regular transfusion therapy, approximately 22% of children receiving transfusions for initial stroke had a second overt stroke, suggesting that regular blood transfusion might not be as effective in preventing secondary stroke in SCD. [17] A recent multicenter study among children on chronic transfusion therapy for prevention of secondary stroke showed that 17.5% had second overt strokes and 27.5% had silent cerebral infarcts. [18]

In low-to-middle–income settings, management of SCD and preventing stroke faces multiple challenges including limited access to blood products, lack of health insurance as most health expenditures are out-of-pocket. [2-4] These barriers make prolonged BTT difficult, necessitating alternative approaches.

Hydroxyurea which induces foetal haemoglobin (HbF) production thereby inhibiting HbS polymerisation, has been shown to reduce vaso-occlusive complications [19-21] and stroke risk. [22-25] A study in Nigeria demonstrated its ability to lower TCD velocities and reduce stoke incidence to 0.27/100 person-years. [26] Several other studies in low-to-middle–income settings, suggested that hydroxyurea therapy could be substituted for chronic blood transfusion for the prevention of primary stroke and to lower risk of secondary stroke in children with SCA. [24-29] The SPIN trial showed that low- (10mg/kg/day) and moderate-doses (20mg/kg/day) hydroxyurea therapy significantly reduced the incidence of primary stroke in Nigerian children with SCA. [30] Similarly, the "Hydroxyurea for secondary stroke prevention in children with sickle cell anemia in Nigeria (SPRINT trial) showed that moderate-doses (20mg/kg/day) HU was not superior to low-dose (10mg/kg/day) for prevention of secondary stroke, as both doses were equally effectively in reducing stroke recurrence rate. [31] The EXTEND trial in Jamaica and the SPHERE Trial in Tanzania, showed that HU therapy alone significantly lowered cerebral arterial velocities in children with SCA. [25, 32] The "Transfusions Changing to Hydroxyurea (TWiTCH)" trial, suggested HU as an alternative therapy for primary stroke prevention after an initial twelve month of chronic transfusion. [27] The study demonstrated that switching to hydroxyurea was non-inferior to chronic monthly blood transfusion in SCA children with abnormal TCD velocity but without severe vasculopathy.

We developed an alternative treatment model combining short-course monthly BTT with HU therapy, transitioning solely to hydroxyurea after discontinuing transfusions. Regular TCD monitoring was done for at least one-year post-transfusion to assess the sustainability of

lowered TCD velocities. The incidence of overt stroke was determined for the same period. This approach adapts the TWiTCH trial by overlapping transfusions with hydroxyurea for 6 months, allowing time to reach the maximum tolerated dose (MTD). This report evaluates the effectiveness of this modified therapy.

METHODOLOGY

This retrospective study was conducted at Lagos University Teaching Hospital (LUTH), Nigeria, serving a state of about 21 million people. Non-imaging transcranial Doppler (TCD) screening became available at the nearby Sickle Cell Foundation Nigeria in 2011, enabling stroke risk assessment in children with SCD aged 2–16 years. A management protocol for abnormal TCD cases was implemented at LUTH, and patient records from the protocol register were reviewed for relevant data. Included for analysis were children with sickle cell disease (HBSS 168, HBSO, and HBSβ°thalassemia, one each) who had two (2) abnormal TCD (TAMMV ≥200cm/s) within 3-month, those with SCA who presented with the first stroke within two (2) months of the stroke (classified as current/recent stroke) or had stroke three (3) months or more with an Abnormal TCD velocity or conditional risk for stroke. All children who were not previously on Hydroxyurea (HU) therapy commenced hydroxyurea (HU) at the beginning of BTT at a dose of 15mg/kg/day with dose escalation every three (3) months until maximum tolerated dose was achieved as practiced in our unit. [33] Those already on HU therapy before commencement of BTT were continued on HU. All the Children continued HU after the discontinuation of BTT. Blood transfusion was done at intervals of 4-6 weeks for 6-8 months. BTT was either simple transfusion or manual exchange blood transfusion. All children had a repeat TCD at the end of transfusion therapy, at 3 months, 6 months and one (1) year after discontinuation of BTT. The main outcomes determined at the end of one year of

discontinuation of BTT were the number of subjects with stroke and number that had lowered TCD, reverted to or remained with abnormal velocity.

Excluded from analysis were children who had more than one stroke at presentation, those who had less than 4 blood transfusions within 6 months or who had an interval of more than 6 weeks between blood transfusions.

Ethical approval was obtained from the Health Research Ethics Committee of LUTH prior to the commencement of the study.

Data were analysed using SPSS version 20.0, with results presented in tables, graphs, and figures. Normally distributed data were reported as mean ± SD, and skewed data as median (IQR). Continuous variables were compared using ANOVA or t-test, and categorical variables with Chi-square or Fisher's exact test. Median values were compared using Kruskal–Wallis, and changes between pre- and post-BTT TCD values with Friedman's test. Kaplan–Meier analysis assessed time to stroke post-BTT. Significance was set at $p<0.05$.

RESULTS

The total number of children enrolled for BTT during the period (February 2012-July 2019) was 208. Of these, thirty-eight (18.3%) were excluded for the following reasons: eight (3.8%) had more than one stroke at the time of commencement of intervention, 19 (9.1%) had 3 or less BTT, 6 (2.9%) were inconsistent with therapy and records were incomplete in 5 (2.4%); the remaining 170 (81.7%) subjects are presented in this report. See figure 1

The mean age was 6.7±3.1years, female constituted 50.6% of the subjects. One hundred and twenty (70.6%) were not on hydroxyurea at the beginning of BTT and were commenced on HU; 40 (23.5%) were already on HU. All subjects were continued on indefinite hydroxyurea therapy at the end of BTT. Other baseline parameters are shown in table 1.

Changes in abnormal TCD before and at the end of study

The changes in abnormal TCD between the beginning of BTT, at the end of BTT and 6-monthly until one year after discontinuation of BTT is shown in Table 2 below χ^2 =315.3, $p < 0.05$. The mean maximum TCD velocity reduced significantly from 221.8 ± 23.3cm/s before BTT to 171.8 ± 30.9cm/s one year post BTT ($F= 93.5$, $p < 0.001$) see supplementary tables and figures. Ninety-two subjects had complete TCD records for the four periods of assessment. Using Friedman Test: (this test for K related ordinal samples), subsequent TCD appears to be improving as subjects continued HU after BTT was discontinued, $p < 0.001$ (Table 3). These changes showed that there was significant improvement in the stroke risk using TCD velocities between pre-BTT and subsequent Post BTT TCDs. The effect sizes were ≥ 0.830 (P values were <0.00 1). There improvement in stroke risk were between the First and third post BTT TCD and between the second and third post BTT TCD. However, there was no significant difference between the first and second post BTT TCDs. See supplementary table.

Further segregation of changes in stroke risk using indication for BTT showed that the greatest improvement occurred in those who had abnormal TCD velocity. This improvement appeared stable through the 12 months post-BTT follow-up in the group with abnormal TCD, there were greater variability in the TCDs in the groups with current or previous stroke. This is presented in table 4.

Outcome for Children on blood transfusion therapy (BTT) one (1) year after Discontinuation of Blood Transfusion

At the end of one-year post-BTT therapy, the number of subjects who developed stroke were determined in 167 of the 170 subjects. In all, 13 (7.8%) had stroke, 2 (1.2%) occurred among subjects whose indication for BTT was Abnormal TCD. The remaining 11 (6.6%) occurred in subjects who had therapy due to current or previous stroke, as shown in table 5**.** Kaplan-Meier analysis showed a 12 month stroke- free survival estimate of 99% in patient with no previous stroke (incidence rate of 1.5 per 100-person year) and 78% in patient with earlier stroke current

and previous), incidence rate of 29.8 per 100-person year). The difference was statistically significant, $p<0.001$. See figure 2 below.

DISCUSSION

Cerebrovascular accident is one of the most devastating complications of SCD with high likelihood of recurrence. The introduction of Transcranial Doppler (TCD) ultrasound as a non-invasive means to predict stroke risk in children aged 2–16 years has significantly advanced primary stroke prevention in this population. Reports from several studies recommend scheduled blood transfusion therapy as an effective intervention for these children. For instance, the Stroke Prevention Trial in Sickle Cell Anemia (STOP) demonstrated a 92% reduction in primary stroke incidence among children with abnormal TCD velocities. [15] A follow-up study revealed that discontinuing chronic transfusion therapy led to reversion from standard or conditional TCD risk to abnormal velocity, with about 5% of patients experiencing stroke when transfusions were halted, compared to none among those who continued therapy. [16]

Despite these promising outcomes, the challenges associated with chronic blood transfusion—particularly in low- and middle-income countries—are significant. The therapy is complicated by the risks of iron overload, blood-borne infections (such as hepatitis B and C), adverse reactions, high costs of delivering the therapy, [34] and limited availability of safe and adequate blood supplies. [35] These factors contribute to the poor acceptance of BTT in regions like Nigeria as noted by Ahmed *et al* in his study in Norther Nigeria. [36] Diaku-Akinwunmi, *et al* [37] noted that 88% of facilities that attempted BTT, could not sustain the program mainly due to inadequate blood supply, poor patient compliance, unavailability of safe blood, lack of funds for processing blood, and absence of staff and facilities.

Furthermore, Lagunju et al [35] reported that only 10% SCA patients requiring chronic blood

transfusion therapy consented in Ibadan, Nigeria, due to high cost of the therapy and scarcity of blood, among other reasons.

In response to these challenges, we designed a six-month regimen that initiated hydroxyurea concurrently with a short course of blood transfusion therapy. The results suggest that beginning hydroxyurea early may limit the reversion to abnormal TCD velocities and reduce subsequent stroke events after the cessation of blood transfusions, particularly in children who initially presented with abnormal TCD readings.

Several modifications to the standard chronic transfusion therapy in STOP trial had been previously explored. For example, the study by Wilimas J, *et al.* [38] administered blood transfusions for 1-2 years, but found that 70% of participants suffered a second stroke within 11 months after discontinuation of therapy. Another study by Cohen et al [39] reduced the transfused blood volume to maintain HbS level at 50% instead of 30% after an initial conventional transfusion therapy of at least 4 years with no observed cerebral infarction in the less intense transfusion arm. Furthermore, the TWiTCH trial, compared continued chronic transfusion with a switch to hydroxyurea (overlapping for 4–9 months) after an average of four years on transfusion therapy. Both groups achieved non-inferior outcomes regarding stroke prevention, with no strokes or progression of vasculopathy observed on magnetic resonance angiography (MRA). [27]

Our findings align with these studies. In our cohort, children with abnormal TCD velocity showed excellent outcomes following a brief period of combination blood transfusion therapy with hydroxyurea for 6-8 months, followed by continuation of hydroxyurea therapy alone. At one year of review only 1.5% had developed overt stroke, although we did not perform Magnetic Resonance Imaging/angiography on any of our patients.

Some critics may argue that a one-year follow-up post-transfusion is too brief for definitive conclusions. However, further analysis of data from the STOP2 trial indicated that most children with abnormal TCD velocities reverted to normal within 4.3 months of transfusions, with gradual stabilisation over the subsequent three months. [40] In that study, 67% of patients converted to normal TCD within one year, a figure that compares favourably with our data where 82% of subjects either achieved conditional risk or normal TCD velocities immediately after transfusion. This finding agrees with the report by Lee et al [41] on extended follow up of the STOP trial. The sustained improvement observed in TCD velocities in our study may be attributed to the continued use of hydroxyurea, which has been shown in multiple studies to reduce elevated cerebral arterial flow velocities and consequently lower the risk of primary stroke. [23, 25, 30, 32, 42, 43]. The incidence rate of stroke and stroke free survival estimate for those with and without previous stroke in our study align with similar studies. The slightly reduced survival estimate for secondary prevention compared to the SPRINT trial may be attributed to the small number of those with stroke in this study. Despite the benefits observed in reducing primary stroke risk, secondary stroke prevention remains more challenging. Even with extended blood transfusion therapy, studies have reported patients still experienced high rates of secondary stroke. [17,44] Other investigators, including work by Greenway et al, [45] and the SWiTCH trial, [46] reported high rates of secondary stroke when switching from chronic transfusion to hydroxyurea. This led to the early termination of the SWiTCH trial because hydroxyurea was found to be inferior for secondary stroke prevention. In resource-limited settings, hydroxyurea appears to also offer some protective benefit. For example, the SPRINT trial demonstrated significant reductions in recurrent stroke events with both low-dose and moderate-dose hydroxyurea compared to no treatment. [31]

A systematic review by Aderinto *et al.* [47] concluded that hydroxyurea alone or as a substitute for chronic transfusion yields variable outcomes for secondary stroke prevention and a pragmatic approach is necessary. The probable reason why chronic blood transfusion does not completely eliminate stroke recurrence is likely due to severe cerebral vasculopathy, which has been documented using MRI and MRA in children with SCD. [48, 49] In fact, some evidence suggests that discontinuing chronic transfusions can worsen vasculopathy, further contributing to recurrent stroke risk. [49-54] It is therefore not surprising that, as in other studies, the rate of recurrent stroke in this report was high and it might not be due directly to the short period of blood transfusion but the degree of cerebral vasculopathy this group of children had. Alternative or prolonged blood transfusion therapies might be required for children with significant vascular pathology for secondary stroke prevention.

The overall evidence suggests that preventing an initial stroke is usually more attainable than preventing recurrent episodes. Given the high prevalence of stroke in Nigerian children with sickle cell anaemia—where up to 21% of those with primary stroke experience recurrence despite hydroxyurea, [55] implementing an early detection strategy using TCD, combined with a short course blood transfusion and long-term hydroxyurea therapy, could substantially reduce morbidity and mortality in high-risk populations.

In summary, while the prevention of secondary stroke remains challenging, our study support intervention with combining short-term blood transfusion and initiation of long-term hydroxyurea therapy can effectively reduce primary stroke risk and improve TCD outcomes in children with SCD. We acknowledge the limitations of our study. Being retrospective, its findings would benefit from validation through a longitudinal study of short-course blood transfusion with sustained hydroxyurea, especially in resource-limited settings. Cerebrovascular pathology assessment was restricted by the absence of MRI/MRA.

Conducting the study in a single tertiary hospital in Nigeria may limit generalisability to other populations. Finally, the one-year post-BTT follow-up may be insufficient to detect late stroke events or assess long-term sustainability of the improved TCD parameters.

Data Availability

Data is provided within the manuscript or supplementary information file if required.

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Conflict of interest

The authors declare that they have no competing interest to disclose

Ethical approval statement

All procedure performed in studies involving human participant were in accordance with the ethical standards of the institution. This study was in line with the laws and regulations of medical research and has been approved by the Ethic Committee of the Lagos University Teaching Hospital.

Authors Contributions

E.T. and A.A. designed the research, interpreted the data and wrote the manuscript. A.J. and U.F. collected and analyzed data; C.O. analyzed data. A.O. and A.S. equally contributed to this work. O.A., N.A., E.E., O.O. and O.E. collected data. All authors contributed to manuscript revision and approved the submitted version for publication.

Patient consent statement

Not applicable

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Table 1: Sociodemographic and clinical characteristics

Table 2: TCD categories in subjects before and after completion of Blood transfusion therapy