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Primary Stroke Prevention in Nigerian Children with Sickle Cell Disease (SPIN): Challenges of Conducting a Feasibility Trial

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Abstract

Background—The majority of children with sickle cell disease (SCD), approximately 75%, are born in sub-Saharan Africa. For children with elevated transcranial Doppler (TCD) velocity, regular blood transfusion therapy for primary stroke prevention is standard care in high income countries, but is not feasible in sub-Saharan Africa.

Procedure—In the first U.S. National Institute of Health (NIH) sponsored SCD clinical trial in sub-Saharan Africa, we describe the protocol and challenges unique to starting a clinical trial in

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this region. We are conducting a single arm internal pilot of hydroxyurea therapy in children with TCD velocity ≥ 200 cm/sec in the middle cerebral arteries. Eligible children will be placed on hydroxyurea (n=40) and followed for 3 years at Aminu Kano Teaching Hospital, Nigeria. Adherence will be measured via the Morisky Scale and adverse events will be determined based on hospitalization.

Results—Originally, a randomized placebo trial was planned; however, placebo was not approved by the local Ethics Committee. Hence a single-arm trial of hydroxyurea will be conducted and five controls per patient with normal TCD measurements will be followed to compare the rate of adverse events to those with abnormal TCD measurements taking hydroxyurea. Using non-NIH funding, over nine months, multiple face-to-face investigator meetings were conducted to facilitate training.

Conclusion—A hydroxyurea trial (NCT01801423) for children with SCD is feasible in sub-Saharan Africa; however, extensive training and resources are needed to build a global patient oriented multi-disciplinary research team with a common purpose.

Keywords

sickle cell disease; hydroxyurea; primary stroke prevention; Nigeria

Introduction

Sickle cell disease (SCD) is one of the most common genetic disease in the world.¹ Approximately 150,000 Nigerian children are born each year with SCD, making it the country with the largest burden of SCD in the world.² Children with sickle cell anemia (Hemoglobin SS or Hemoglobin S beta zero thalassemia (HbS/ β^0); SCA) have one of the highest rates of ischemic stroke of any group of children, with an incidence of 285 per 100,000 person-years³ in the United States, prior to effective primary stroke prevention. Given the importance of reaching developmental milestones, and the necessity of formal education in childhood, the lifelong adverse impact of strokes in children is tremendous. The incidence of strokes in children with SCA in the United States has dropped exponentially with the routine use of TCD to identify children at risk, coupled with regular blood transfusion therapy.⁴ However, in low income countries, the availability to prevent strokes for children with high TCD measurements is extremely limited.

The critical unanswered question in low income countries is whether the benefits of hydroxyurea (HU) therapy will outweigh the potential risks of giving a myelosuppressive agent to children in a region with a higher rate of bacteremia and malaria.⁵ The burden of SCA among children is underscored by the estimate of 7,500 children each birth year cohort that will have a stroke by 14 years of age (approximately 150,000 children with SCA are born in Nigeria per year,² of which 11% are expected to have strokes⁶ and we estimate that only 75% of the cohort will reach their 14th birthday).

Addressing the pressing need to prevent strokes in children with SCA in Nigeria, we assembled an international multidisciplinary team of pediatricians, hematologists, radiologists, and neurologists from the United States, United Kingdom and Nigeria. The

overall goal of the Stroke Prevention in Nigeria (SPIN) Trial (NCT01801423) is to determine whether HU therapy can be used as a primary stroke prevention strategy for children with elevated TCD measurements in Nigeria. The internal pilot will provide vital information necessary for a Phase III Trial. The purpose of this article is to describe challenges and benefits of initiating the first NIH sponsored clinical trial in SCD in sub-Saharan Africa.

Methods

Study design

The SPIN Trial is a single site, single arm trial, internal pilot in which children ages 5 to 12 years with elevated TCD measurements receive low dose HU therapy for 3 years. Specific aims of the trial include: 1. Determine the adherence rate to daily HU therapy in children with SCD and elevated TCD measurements; 2. Assess the safety of HU therapy, as it relates to infection associated with hospitalization and mortality; and 3. To complete the necessary preparations for a definitive Phase III Trial.

Study Setting

Aminu Kano Teaching Hospital (AKTH) is a 500-bed tertiary level facility affiliated with Bayero University and is located in Kano, the second largest metropolis in Nigeria (estimated 2006 population: 9.4 million).⁷ The pediatric SCD clinic is housed within the Department of Pediatrics and is staffed by 4 attending and 3 resident physicians. The clinic has a total patient pool of 1,700 children with SCD, with approximately 70 children with SCD seen weekly on each clinic day.

Primary Aim and Endpoint

The overall goal of this internal pilot is to determine the acceptability of low dose HU therapy (approximately 20 mg/kg/day), based on the measure of adherence to HU therapy, for primary prevention of strokes. The primary outcome measure is adherence to daily administration of HU using a monthly assessment of the Morisky Medical Adherence Scale.⁸ If the monthly average adherence is less than 55% based on an average score of at least 5 or more (rating as good), alternative strategies will be considered for the definitive Phase III Trial.

Secondary Aims and Endpoints

The secondary aim is to establish a safety protocol for using low dose HU therapy for primary prevention of strokes in a clinical trial setting for three years in a low income country. We will evaluate the use of a low dose HU therapy standard safety protocol, similar to the NHLBI Baby HUG study.⁹ We compared the frequency of severe adverse events and HU toxicity-related events associated with hospitalization in participants receiving HU (n=40) to those who were screened and had normal TCD measurements (n=210) (Figure 1). Our secondary hypothesis was low dose HU therapy for primary prevention of strokes in children with an elevated TCD measurement is associated with no significant increase in morbidity or mortality when compared to children not receiving HU therapy with TCD measurements < 199 cm/sec.

Justification For Controls

The expected rate of SCA complications for children receiving or not receiving HU therapy at AKTH or anywhere in sub-Saharan Africa is unknown. The primary reason for controls was to have a comparison group to assess potential HU related toxicities, such as hospitalization for a) any cause; b) vaso-occlusive pain; and c) fever (temperature greater than 38.0°C) associated with suspected or confirmed infection based on CDC criteria¹⁰ and WHO classification.¹¹ The number of control participants primarily reflects the maximum number of participants the study could accommodate with the budget.

Safety and Adverse Event Considerations

For individuals receiving HU therapy, monitoring for unanticipated adverse effects will be performed 2 weeks after starting the therapy, and then every four weeks for 36 months. An interim utility analysis at roughly 50% of participant enrollment is planned. At that time, if the point estimate of the difference of the one-year stroke rate is consistent with detriment (difference of the rate = 0; trial result vs. historical control result), then the Data Safety Monitoring Committee will consider terminating the study early for overall lack of treatment effect. We excluded children less than five years of age because of the higher rate of bacteremia^{12,13} and malaria⁵ in that age group, the unknown effect of HU therapy on the rate of infection in low income countries, and the absence of a stable liquid formulation of HU that did not require refrigeration.

Adverse events were scored using the Common Toxicity Criteria for Adverse Events (CTCAE) 3.0 of the National Cancer Institute and the standard nomenclature for defining the causal relation between the adverse event and study drug (unrelated, probably not related/remote, possibly related, probably related, definitely related).¹⁴

Sample Size Estimation

The primary endpoint of the internal pilot was adherence to HU therapy. Our primary hypothesis was that families will participate in a primary prevention stroke trial with an adherence rate of 80% for daily administration of HU. The sample size estimation was completed using the one-sample exact binomial test. The proposed sample size of 40 provided at least 90% power to detect a difference in adherence of 25% (study adherence rate = 80% vs. historical control⁴ adherence rate = 55%) with two-sided type I error = 5%. If the adherence rate is less than 55%, alternative strategies will be considered for the definitive Phase III Trial.

Statistical Analysis

Demographic features of participants enrolling in the SPIN Trial were compared to controls. Descriptive statistics will include means and standard deviations for continuous data and percentages for categorical data. As this is the first trial of its kind in Nigeria, we do not know the rate of participation for those that were approached. Point estimates $\pm$ 95% confidence intervals (CI) of the acceptability of entering the trial will be computed. The exact 95% CI of adherence rate based on binomial distribution will be reported. For neurological measures, all children will have a standardized neurological examination, the

Pediatric Stroke Outcome Measure (PSOM) at baseline, after any neurological event, and at study exit.¹⁵

Definitive Phase III Trial

The primary hypothesis for the definitive phase III trial was: **low dose HU therapy (approximately 20 mg/kg/day) will result in a 60% relative risk reduction when compared to historical controls from the STOP Trial).**⁴ When compared to the incidence rate of overt strokes in the observation arm of the STOP Trial,⁴ 89 children with an elevated TCD measurement must be enrolled and followed for three years to obtain a 90% power, with significance level equal to 0.05 and assumed dropout rate of 10% over the course of the trial. The primary endpoint for the definitive Phase III trial is an overt stroke defined clinically. We chose this strategy because in the original STOP I study all participants that met the criteria for a primary end point (clinical stroke and evidence of an infarct on magnetic resonance imaging) had evidence of a focal neurological deficit upon presentation⁴ and magnetic resonance imaging is not feasible to perform in low income countries. The primary factor determining the presence of stroke will be neurological deficit that persists for >24 hours and a clinical picture that is consistent with stroke.

After an endpoint is reached, participants will be withdrawn from the study and their treatment will be at the discretion of their physician and family. After completion of the study, participants will be given the option to continue or stop the study drug based on a conversation with their physician.

Results

Unanticipated Challenges

Several barriers occurred before the first participant was enrolled. The initial unforeseen challenge was the reluctance of the AKTH Ethics Committee to approve a trial with no treatment for children with elevated TCD measurements. Prior to the start of the trial, TCD screening was not routinely available for all children with SCA. The trial required the purchase of TCD machine and allowed routine screening in the SCD clinic. The health care team at AKTH described the standard care of children with elevated TCD measurements as not including regular blood transfusion therapy. The AKTH research team clinical experience of having relatively few children with an elevated TCD measurement being placed on regular blood transfusion therapy reflects the recent experience in another tertiary care center in Nigeria where over a course of five years, none of the children with an elevated TCD measurement received regular blood transfusion.¹⁶ We modified our original study design from a feasibility trial (external pilot) to a single-arm internal pilot trial with construction of a control group, i.e., individuals that were screened for an elevated TCD measurement, but were found to have a normal value.

Travel to the US proved more challenging than expected. Two individuals were initially denied a visa to travel to Vanderbilt University for a one month training course. One of these two was ultimately granted a visa, while the second one was never granted a visa.

As is the case in most trials that include imaging studies as part of eligibility assessment, standardization of the imaging procedure is critical. Our original goal was to have two ultrasound technicians receive the training for TCD assessment; however, local clinical practice is such that imaging procedures are completed by physicians and not ultrasound technicians. We elected to have two radiologists trained to perform TCD assessment with rigorous TCD training sessions conducted at Guys and St. Thomas. Ultimately, imaging standards were met for interrogating the middle cerebral artery (MCA), but were not met for the terminal portion of the internal carotid. We limited the eligibility criteria in the feasibility trial to include an elevated TCD measurement in the MCA.

Unanticipated Benefits

The purchase of a dedicated TCD machine, coupled with training of the radiologist and introduction of TCD screening for SPIN trial participants, has led to the adoption of routine TCD screening as standard of care for all children with SCD attending AKTH. Though an effective intervention for stroke prevention is the focus of the trial, families have already benefitted from anticipatory guidance about stroke in SCD and increased awareness of the possibility of strokes. These benefits of being in a clinical trial are consistent with findings by others that clinical trials may improve the clinical care of patients not part of the trial through improvement in clinical protocols.¹⁷

Initial team building activities were critical to facilitate the initiation and completion of the trial. The NIH funding did not have sufficient resources to accommodate three face-to-face meetings between the two investigator teams (US and Nigeria) within the first 12 months of funding. Further, there were insufficient funds to pay for unanticipated impediments for moving the trial forward, such as extended training of the radiologists for TCD assessment or purchasing a dedicated TCD machine and provision of ongoing education of the research staff, all of whom were new to the process of conducting trials. Institutional resources from Vanderbilt University, coupled with awards from two foundations, the Doris Duke Charitable Foundation and the Aaron Ardoin Foundation were critical components that prevented the trial from stalling. A major advantage of these foundation funds was the ability to shift funds where and when the needs arose, in a timely fashion.

Another unanticipated benefit of the trial was the additional educational opportunities afforded to members of the AKTH research team. Specifically, the site investigator at AKTH received the David Satcher Award at Vanderbilt University, a full tuition award that supports a Master's of Public Health. In addition, four members of the AKTH research team, including two hematology fellows at AKTH, are participants in the two-year New York University School of Medicine Cardiovascular Research Training Institute (CaRT; 5D43TW009140-03), a collaborative program funded by the Fogarty International Center and NIH with New York University School of Medicine, and the University of Ghana School of Public Health. Four senior members of the study team also attended the month-long annual Vanderbilt Institute for Research Development and Ethics (VIRDE) course designed to facilitate grant development and research governance for patient-oriented research in global health.

Current Study Enrollment Status

During the first 9 months of enrollment, a total of 260 participants signed the informed consent for screening, of which 192 have been screened with TCD. 175 and 17 were found to have normal TCD measurement and high TCD values, respectively. Seventeen participants were eligible for HU therapy (Table I), of which 15 have been consented/assented for participating in the trial. Two parents of children eligible for treatment refused.

Preliminary results at 3 months of study entry—At month three, 100% of the participants who reached this milestone (n=11) demonstrated average to high adherence (Morisky scale 6-8 points). Ten of the eleven children had decreased TCD measurements below the critical threshold of 200 cm/sec while on HU therapy at the 3-month follow-up (Table II). The parental report of adherence to therapy was consistent with an increase in MCV from baseline to 3 months after starting HU therapy. The MCV increased in 10 out of the 11 participants with 5 out of the 11 having an MCV above 100fl. Four participants have not yet reached the 3-month milestone. No serious adverse events (Table II) and only one adverse event were noted in a participant who became dehydrated secondary to Shigella-related enteritis and was treated with intravenous fluids. No evidence of myelosuppression was present at the time of the patient's hospitalization. Of the 140 patients who are eligible to be controls thus far, 72% (101 of 140) parents have consented to be followed (Table III).

Implications of preliminary data on future phase III Trial—Based on the dramatic and unforeseen response in decrease of TCD velocity within 3 months of starting HU therapy and the strong ability and motivation of our health care team at the study site, we elected to review our phase III study design. Ultimately, we elected to pursue a single arm phase III trial with a low fixed dose of HU therapy for a total of 36 months. All eligible children will receive low dose HU therapy at the beginning of the study. TCD evaluation will be repeated at 3 months, all children with a drop in TCD measurement below 200 cm/sec in both vessels will continue on low dose HU therapy. Children with persistently elevated measurements above 200 cm/sec on either side will have a repeat TCD at 6 months. If the TCD measurements for participants in either vessel continue to be equal to or above 200 cm/sec at the 6 or 12 month TCD evaluation, the participant and family will be given the following options: withdraw participant from the study and receive the best therapy available at the discretion of the parents and the hematologist or pediatrician; or stay on the trial and continue the same protocol with no change in dose escalation.

We elected to continue HU therapy in children with persistently elevated TCD measurements because there were few therapeutic alternatives available. Further subgroup analysis from the STOP Trial demonstrated that approximately 20% of the participants that remained on blood transfusion therapy had persistently elevated TCD measurements for a mean of 2.4 years with no strokes.¹⁸

Discussion

Approximately 75% of the children with SCD are born in sub-Saharan Africa where the clinical research infrastructure is minimal and the opportunity to decrease morbidity and mortality are greatest.¹⁹ As an illustrative example, approximately 1,400 children with SCD

are born per year in the US,²⁰ 14,000 per year in Ghana²¹ and 150,000 per year in Nigeria² and yet, to our knowledge no NIH-funded SCD clinical trial has ever been sponsored in this region. This mismatch between research capacity and unimaginable SCD-related suffering for children in sub-Saharan Africa represents a rare opportunity to combine patient-oriented research with humanitarian efforts.

Our strategy for undertaking this trial was to invest in a team of investigators to work on a common research question. We took this approach based on our belief that this tactic is more sustainable and less susceptible to the impact of a loss of an individual team member.

To implement this strategy for training, we received funding from the Doris Duke Charitable Foundation and the Aaron Ardo Foundation for Sickle Cell Anemia, as well as pre-existing funds from the Burroughs Wellcome Foundation and endowed funds from Vanderbilt University School of Medicine. The new foundation awards provided both critical and timely financial support to bring the international teams together. As a direct result of the foundation funding, three face to face meetings were held within the first nine months of the start of the trial. These meetings were particularly critical because the members of the AKTH team lacked experience in initiating and conducting clinical trials and were unfamiliar with research governance principles of patient-oriented research. Training on fiscal responsibility and creating regulatory binders and a manual of operations had to be performed. Strategies for work flow were discussed and refined in person and revised after initial trial and error. Additional funds were used to hire a research nurse and research assistant, as the NIH funds were insufficient to cover these costs. Ultimately through three non-NIH funding sources, and limited NIH funding, we were able to lay the ground work for a successful clinical trial in a Nigerian academic medical center where no previous NIH sponsored trial has been conducted.

Based on early results of our feasibility trial, conducting SCD clinical trials in this region of the world is a viable option for patient oriented research. However, such effort requires the infusion of significant resources to educate the in-country team of investigators and research staff ensuring fidelity to study protocol and appropriate research governance. Ultimately conducting SCD patient-oriented research in sub-Saharan Africa will not only benefit the region of the world with the greatest burden of the disease, but should provide insight into optimal strategies for clinical care for individuals with the disease in high income countries.

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Figure 1.
The participant flow diagram of the Sickle Cell Disease Stroke Prevention in Nigeria (SPIN) Trial.

Table I
Demographic features of the participants enrolled in the Sickle Cell Disease Stroke Prevention in Nigeria (SPIN) Trial during the first 12 months of open enrollment

	N	Normal ^c (< 170 cm/sec)N=132	Conditional ^c (170-199 cm/sec)N=14	Abnormal ^c (≥ 200 cm/sec)N=17
Gender Female (%)	161	49%	79%	56%
Age^a	162	8 (6, 10)	7 (6, 8)	6 (5, 7)
Ethnic group				
Hausa-Fulani		90%	93%	81%
Yoruba	142	3%	0	12%
Igbo		1%	0	0
Other		6%	7%	6%
Highest Education, head of household				
None/Unknown		4%	0%	0%
Primary	144	3%	17%	35%
Secondary		18%	93%	41%
Tertiary		74%	0%	24%
Household Income per year in US dollars^b				
<\$3500		1%	0%	29%
\$3500- <\$5000	130	18%	16%	21%
\$5000 - <\$6100		26%	17%	21%
\$6100		56%	67%	29%
Marital status of primary caregiver	144			
Married n (%)		97%	100%	94%
Relationship of primary caregiver				
Mother	144	33%	21%	35%
Father		64%	64%	53%
Other relative		3%	14%	12%

^a Median (interquartile range)

^b Note: 1 US dollar ≈ 163 Nigerian Naira

^c TCD- Transcranial doppler velocity measurement.

Radiological and laboratory results of the 11 participants within the first 12 months of the Sickle Cell Disease Stroke Prevention in Nigeria (SPIN) Trial that were on hydroxyurea for at least 3 months.

Table II

S/No	TCD velocity in cm/sec				Markers of toxicity (count*10 ⁹ /l)				Markers of adherence			
	Right MCA		Left MCA		WBC		ANC		MCV (fl)		HbF-g/dl	
	BL	3M	BL	3M	BL	3M	BL	3M	BL	3M	BL	3M
1	165	151	211	161	8.8	7.3	3.15	3.4	108.9	114.8	25.1	
2	208	208	193	168-	6.7	8.0	3.02	2.5	88.6	99.2	15.5	
3	191	167	208	181	8.6	11.9	3.13	6.3	82.5	85.7	10.4	
4	204	182	200	182	19.2	15.7	7.87	7.1	92.1	102.4	18.9	
5	182	174	231	253	17.8	14.9	8.5	7.0	94.3	96.9	9.1	
6	181	157	220	164	24.5	16.8	12.7	11.9	94.9	103	18.3	
7	200	164	168	182	10.8	10.1	6.0	6.2	73.2	55.3	5.5	
8	248	259	128	163	7.4	14.8	3.0	9.0	92.9	100.6	16	
9	240	173	208	202	19.0	13.9	9.8	5.7	80.4	92.1	12.6	
10	234	176	214	189	11.9	12.6	5.4	7.2	91.2	92.7	6.3	
11	215	197	186	169	21	23.2	9.2	10.4	97.7	102.9	4.0	

TCD-transcranial Doppler ultrasound, MCA-middle cerebral artery, BL-baseline, M-month, MCV-mean corpuscular volume, WBC-white blood cell, ANC-absolute neutrophil count, HbF-hemoglobin F; Hemoglobin F levels were not done at baseline.

Table III
Eligibility criteria for the Sickle Cell Disease Stroke Prevention in Nigeria (SPIN) Trial

Inclusion Criteria	Exclusion Criteria
<ol style="list-style-type: none"> 1 Diagnosis of HbSS or HbSB⁰ based on hemoglobin electrophoresis results. 2 Informed consent from a parent or legal guardian. 3 Age between 5 and 12 years. 4 Able to swallow a capsule. 5 Successful completion of screening procedures (cerebral blood flow velocity > 200 cm/sec in the terminal portion of internal carotid or middle cerebral artery). 	<ol style="list-style-type: none"> 1 Prior overt stroke (a focal neurological deficit of acute onset) by history, focal neurological deficit on standardized neurological examination. 2 Significant cytopenias [absolute neutrophil count (ANC) <1,500/uL, platelets <150,000/uL, reticulocytes <80,000/uL, unless the Hb is > 9g/dL]. 3 Renal insufficiency (creatinine > 0.8 mg/dL). 4 Other significant organ system dysfunction. 5 Other contraindication to HU. 6 Patients for whom HU therapy is under consideration to treat their SCA will be excluded.

Table IV
Integrated team approach and capacity building of the Sickle Cell Disease Stroke Prevention in Nigeria (SPIN) Trial

APPROACH:	OUTCOME:
1. Meetings between the Investigators at Vanderbilt University and Aminu Kano Teaching Hospital	Three face-to-face meetings in the first 9 months of the 6 members of the AKTH team and the 5 members of the Vanderbilt team (London and Nashville). Weekly teleconference calls with members of the team.
2. Capacity for screening and enrollment	We have already screened 178 children and enrolled 92% (12 of 13) children with an elevated TCD measurement, thereby demonstrating our capacity to screen, identify and enroll children in a single arm trial in the approximately 9 months since the trial opened.
3. Commitment to developing research capacity in Kano, Nigeria.	The MPIs visited AKTH in 2011 and concluded that the strength of the clinical science was heavily dependent on developing in-country capacity for clinical and translational research.
4. Capacity building for the research team In Kano, Nigeria	Funding from the Doris Duke Charitable Foundation for a two-year research training award to provide mentoring and hands-on experience for key members of the SPIN Trial team. Attendance at the month-long annual Vanderbilt Institute for Research Development and Ethics (VIRDE) course for two consecutive years. Three members of the stroke trial team spent a month at Vanderbilt in October 2013 as part of the VIRDE program. Four members of the AKTH team have been accepted to participate in a two-year clinical research program sponsored by NIH, with a focus on developing independent investigators: the Cardiovascular Research Training (CaRT) project.
5. Competency of Study Investigators in performing study procedures	Study radiologists at AKTH completed formal training and certification for competency to perform TCD screening in children with SCD at Guy's Hospital, London, England
6. Quality assurance and data archiving	All TCD images will be saved and reviewed by a consultant with specific expertise in TCD screening in children with SCD.
7. Adequate infrastructure and study personnel for the Phase III Trial	Pre-established infrastructure created for the single arm SPIN trial can be scaled up for the randomized trial, as the database, staff training and IRB approval have been completed and the same personnel will be working on this trial. An established and productive research team at AKTH, the location of the current application, with multiple prior publications and history of funding, including an extramural funded project with AKTH faculty to assess the prevalence of asthma in SCD in Kano, Nigeria (Burroughs Wellcome Foundation).