Feasibility Trial for Primary Stroke Prevention in Children with Sickle Cell Anemia in Nigeria (SPIN Trial)

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Abstract

The vast majority of children with sickle cell anemia (SCA) live in Africa, where evidence-based guidelines for primary stroke prevention are lacking. In Kano, Nigeria, we conducted a feasibility trial to determine the acceptability of hydroxyurea therapy for primary stroke prevention in children with abnormal transcranial Doppler (TCD) measurements. Children with SCA and abnormal non-imaging TCD measurements (200 cm/s) received moderate fixed-dose hydroxyurea therapy (~20 mg/kg/day). A comparison group of children with TCD measurements < 200 cm/s was followed prospectively. Approximately 90% (337 of 375) of families agreed to be screened, while 92% (25 of 27) of those with abnormal TCD measurements, on two separate occasions, enrolled in the trial. No participant elected to withdraw from the trial. The average mean corpuscular volume increased from 85 fL at baseline to 101.3 fL at 24 months, demonstrating adherence to hydroxyurea. The comparison group consisted of 210 children, of which four developed abnormal TCD measurements, and were started on hydroxyurea. None of the monthly research visits were missed (n = total 603 visits). Two and ten deaths occurred in the treatment and comparison groups, with mortality rates of 2.69 and 1.81 per 100 patient-years, respectively (p = 0.67). Our results provide strong evidence, for high family recruitment, retention, and adherence rates, to undertake the first randomized controlled trial with hydroxyurea therapy for primary stroke prevention in children with SCA living in Africa.

Keywords

INTRODUCTION

One of the most feared and devastating complications for children with sickle cell anemia (SCA) and their family is a stroke. In children with SCA, strokes are now mostly preventable. Abnormal transcranial Doppler (TCD) ultrasound screening coupled with regular blood transfusion therapy has resulted in a significant drop in the rate of strokes.[1, 2] In one tertiary care center in the United States, the stroke incidence rate dropped by approximately 10-fold (from 0.67 to 0.06 strokes per 100 patient-years) after initiation of TCD screening, with regular blood transfusion therapy for those with abnormal TCD measurements.[2]

Unfortunately, in Africa, no systematic approach has been undertaken to prevent strokes in children with SCA. Nigeria is the country with the largest population of SCA in the world (approximately 150,000 births of children with SCA per year),[3] compared to the United States (approximately 1,700 children with SCA born each year).[4, 5] Major obstacles for primary stroke prevention in Nigeria include, but are not limited to: the lack of access to TCD equipment and inadequate training of staff in detecting abnormal TCD measurements. Possibly the greatest challenge to primary stroke prevention in Africa is the inability to replicate the standard of care for primary stroke prevention present in high-income countries, specifically regular blood transfusion therapy for at least a year.[6] Regular blood

transfusion therapy for stroke prevention is not accepted as an option for most parents of children with SCA because of concerns about cost, safety of blood transfusion and limited blood supply.[7]

Given that regular blood transfusion therapy is not a viable option for primary stroke prevention for children living in Africa, we conducted a single-arm feasibility trial to determine the acceptability of moderate fixed-dose hydroxyurea (~ 20 mg/kg/day) for primary stroke prevention in Nigerian children with SCA (NCT01801423; grant number 1R21NS080639). We tested the primary hypothesis that moderate fixed-dose hydroxyurea therapy is a feasible intervention for children with SCA and TCD measurements   200 cm/s. We also established strategies for hydroxyurea toxicity monitoring in Africa and creating stroke prevention teams in Nigeria beyond the setting of the clinical trial.

METHODS

Study Design

Ethical approval for the study was obtained from the Institutional Review Boards (IRBs) of Aminu Kano Teaching Hospital (AKTH) and Vanderbilt University Medical Center. Regulatory approval was provided by the National Agency for Food and Drug Administration and Control (NAFDAC) in Nigeria. Written informed consent and assent were obtained prior to screening. The single-arm and single-site feasibility trial was opened for enrollment in April 2013, approximately 6 months after receipt of funding. Enrollment was completed in October 2014. The trial was conducted at the pediatric sickle cell disease (SCD) clinic of AKTH located in Kano, Nigeria. From April 2013 to October 2014, we performed screening procedures on all consented children with SCA to determine those eligible for study therapy. The data were locked for analysis in November 2016.

The inclusion criteria for the moderate fixed-dose hydroxyurea therapy included: 1) confirmed diagnosis of HbSS or HbSB^0, referred to as SCA; 2) two independent TCD time-averaged mean velocity (TAMV) readings of   200 cm/s in the middle cerebral artery (MCA) using the non-imaging technique, based on validated assessments conducted by two study radiologists or a single measurement > 220 cm/s; 3) age 5 to 12 years (including the peak age of onset of strokes in SCA, approximately 6 years);[8] 4) ability to swallow an empty(similar size to study therapy) pill capsule prior to treatment; and 5) acceptance of hydroxyurea therapy with minimum follow-up of 12 months on the study therapy. All eligible participants for the trial were offered regular blood transfusion therapy for primary stroke prevention.

The exclusion criteria included: 1) prior history of overt stroke, or concern for moderate to severe neurological deficit based on a positive validated "10 questions" screening;[9, 10] 2) other significant organ system dysfunction (any contraindication to hydroxyurea therapy); 3) history of seizures or diagnosis of epilepsy; 4) prior placement on regular blood transfusion or hydroxyurea therapy; 5) significant cytopenias (absolute neutrophil count < 1.5×10^9/L, platelets < 150×10^9/L, reticulocytes < 80,000/μl when hemoglobin level is > 9 g/dL).We excluded children less than 5 years of age due to the high mortality rate as well as malarial and bacterial infections seen in this age group in Nigeria.[11–14]

The comparison group consisted of individuals who signed the informed consent, had TCD measurements <200 cm/s in the MCA, and agreed to be followed prospectively. The comparison group was followed with at least one standard care visit per year with planned quarterly interim telephone calls to assess status.

Certification in TCD ultrasound scans technique and neurology examination

Initially, two Nigerian radiologists recruited for the trial were trained and certified after demonstrating reproducibility in assessment of velocity in the MCA with an experienced ultrasonographer in the United Kingdom (who has been teaching non-imaging TCD procedure for two decades). The two on-site radiologists on the trial were certified only in assessing velocity in the MCA using a non-imaging TCD machine (Acuson Sequola, Siemens Healthcare GmbH, Germany). For the TCD training, we used volunteers both with and without SCA, including several with prior abnormal TCD values. After completion of training, one of the two trial radiologists was responsible for training and certifying three non-radiology Nigerian physicians (medical officers) to determine TCD measurements in the MCA only. For the trial-certified radiologist (trainer), we determined the intra-observer coefficient of variation by repeating the TCD measurements in the same participant on the right and left MCA in study participants within 3 hours. Spearman's rank correlation (r) was performed on the two measurements made by the trainer on the right and left side. The minimum acceptable correlation for the trainer's two measurements on each side was set as 0.90, with an expected lower bound correlation between the trainer and trainee of 0.765 (85% of the trainer's correlation in the same individual performed only hours apart).

The sample size for the TCD training for the trainees, as compared to the trainer, was calculated using Spearman's rank correlation. Sample sizes of 42 and 31 paired measurements between the trainer and each trainee were associated with a power of 90% and 80%, respectively, based on the correlation between the trainer and trainee exceeding the lower bound of 0.76. Based on these sample size calculations, we aimed for each medical officer (trainee) and the trainer to have at least 40 paired TCD evaluations. All research physicians were trained and certified on the Pediatric NIH Stroke Scale (PedNIHSS), a validated, standardized neurological examination that was used for the study.[15] Each TCD-certified medical officer performed a minimum of 10 neurological examinations in children, which were verified by experienced pediatric neurologists (L. Jordan, F. Kirkham). The SCA Primary Stroke Prevention Team consisted of a pediatrician, ultrasonographer (medical officer) and pediatric nurse. The clinical team was larger but the team interacted with the children and family daily.

Measurements of feasibility of hydroxyurea therapy required for a phase III trial

Feasibility of the trial was measured with three outcomes: recruitment, retention, and adherence rates to hydroxyurea therapy. Recruitment rate was measured based on the proportion of participants approached that signed informed consent divided by the number of participants approached. Retention rate was measured based on the proportion of participants that elected to remain in the trial. Adherence rate was measured directly by an increase in mean corpuscular volume (MCV) (with an expected increase of at least 10 femtoliter (fL), and indirectly by the modified Morisky Medication Adherence Scale score

(MMAS-8).[16–18] The MMAS-8 was previously validated for assessment of hydroxyurea adherence in children with SCA.[16] The MMAS-8 is scored as follow: high adherence (8 points), average adherence (6 to 7 points), and poor adherence (0 to 5 points).

Sample size for feasibility trial

After funding of the trial, the AKTH IRB rejected a randomized controlled trial with a treatment and placebo arm of 40 abnormal TCD measurements. Consequently, we elected to enroll 25 participants with abnormal TCD measurements to receive fixed dose hydroxyurea therapy (treatment group) and 210 participants with TCD measurements < 200 cm/sec to be followed prospectively (comparison group). The final sample size was based on budgetary restraints.

Safety monitoring and evaluation for participants receiving moderate fixed-dose hydroxyurea therapy

Monitoring for unanticipated adverse effects was performed two weeks after starting hydroxyurea therapy for all participants; thereafter, monthly. A missed follow-up visit was defined as not being evaluated within two weeks of the scheduled monthly visit. An interval history of medical events and laboratory values was obtained monthly during the planned research visits for each participant. We also interviewed parents during monthly follow-up visits for participants receiving hydroxyurea therapy for assessment of indicators of stroke and adherence. Participants on hydroxyurea therapy were monitored with scheduled research visits monthly for cytopenias. We defined an adverse event as adverse reactions that are expected complications in children with SCD (including pain, acute chest syndrome, priapism, sepsis, splenic sequestration, hospitalization, and blood transfusion). We defined severe adverse events as those leading to prolonged hospitalization beyond seven days, admission into the intensive care unit, near death, or death. We used the Common Toxicity Criteria for Adverse Events.[19]

Safety evaluation for participants in the comparison group

On an ongoing basis (typically monthly), we reviewed the hospitalization records for individuals in the comparison group and contacted the parents with a goal of at least quarterly to determine if their child was hospitalized, and if so, for what reason. We recorded an annual visit and TCD assessment (as standard care) for participants in the comparison group. When possible, we sought medical records to better characterize the reason for hospitalization and whether the child was still alive (and if not, the cause of death).

Baseline immunization status in participants screened to participate in trial

Immunization cards, if available, were confirmed for immunization status for *Haemophilus influenzae* type b (Hib vaccine) and pneumococcal conjugate vaccine (PCV-13 vaccine). Otherwise, medical records or parent recall were recorded. Vaccination coverage for Hib and PCV-13 was defined only in cases in which the written record of the immunization matched the oral history. Complete vaccination was defined as three documented doses for Hib vaccination and at least one documented dose of PCV-13.

Statistical analysis

We summarized descriptive statistics using median and interquartile range (IQR) for continuous data and percentages for categorical data. The comparison of baseline characteristics between the study and comparison groups was performed using Wilcoxon rank sum test for continuous variables and Pearson's Chi-Square test for categorical variables. Paired Wilcoxon rank sum tests were performed to examine the change in laboratory values from baseline to 3 months and from baseline to 12 and 24 months. All tests used a 2-tailed probability, with p-values < 0.05 considered statistically significant. All analyses were performed using R version 3.1.2.

RESULTS

Demographics of treatment and comparison group

A total of 25 participants were initially enrolled in the treatment group and received moderate fixed-dose hydroxyurea therapy (range: 16.5 to 23.5 mg/kg/day, based on the weight of the child and the capsule size). A total of 210 participants were enrolled in the comparison group. The median ages of the study participants and comparison group were 8 and 6.8 years, respectively. No statistically significant differences were observed in age, sex, ethnicity, height, and weight between the study and comparison groups, Table I. The median (IQR) for follow-up for the treatment and comparison group was 2.14 years (1.75, 2.69) and 2.11 years (1.86, 2.48), respectively.

Good reproducibility in trainer and successful TCD training in non-radiologists

The trainer, a board certified Nigerian radiologist, demonstrated reasonable ability to reproduce their results with paired examination in the same participant. The trainer's coefficient of variation obtained in 21 participants for the right and left MCA was 7.6% and 12.0%, respectively, in the same participant and with the second evaluation occurring within 3 hours after the first evaluation.

The correlation coefficient between the trainee and trainer for the right and left MCA was high. In the right MCA, each trainee had a correlation coefficient greater than 0.90 ($n = 40$). For the left MCA, the correlation coefficient for each pair was greater than 0.83 for all three trainees ($n = 40$).

Enrollment and retention rates were high

A total of 375 families were approached to be screened for abnormal TCD measurements, of which 90% (337 of 375) consented for screening, 8% (27 of 337) had two consecutive abnormal TCD measurements and were eligible for therapy, and a total of 92% (25 of 27) participated in the trial and received hydroxyurea therapy. A total of 284 parents of children were approached to be in the comparison group, of which 74% (210 of 284) consented to enroll, Figure 1. None of the families of children with abnormal TCD measurements ($n = 27$) agreed to regular blood transfusion therapy for primary stroke prevention. As per protocol, all participants in the treatment group were expected to attend monthly research visits for interval history, physical examination, and laboratory surveillance for assessment of hydroxyurea toxicity. None of the scheduled visits were missed ($n =$ total 603 visits).

None of the participants in the treatment group withdrew voluntarily from the trial (retention rate 100%). One participant was administratively withdrawn from the study due to development of progressive renal failure after enrolling in the trial. During follow-up visits, four participants in the comparison group converted to abnormal TCD velocities at 8, 10, 15 and 19 months after enrollment, respectively.

Adherence rates to hydroxyurea therapy and monthly research visits were high

Both direct laboratory measures and the parents' assessments of adherence were high. An increase in MCV by at least 10 fL was observed in 22 of the 25 participants, with the mean MCV increasing from 85 fL at baseline to 96 fL, 98 fL, and 101 fL at 3, 12, and 24 months, respectively. In three participants without an increase of at least 10fL in the MCV values; one participant had an increase in their baseline hemoglobin of 1.9 g/dl, 12 months after the start of hydroxyrea, and the other two had baseline MCV measurements of 97 fL. There was an increase in the mean hemoglobin F (HbF) level from 8.3 % at month 1 to 11.6%, 13.6%, and 14.3% at 3, 12, and 24 months, respectively. Parental report of adherence based on the modified MMAS-8 was high, with 100% of participants demonstrating average to high adherence to hydroxyurea therapy with scores > 6 points. The mean Morisky score for the feasibility trial was 6.88, with 10th percentile of 6.62, 50th percentile of 7, and 80th percentile of 7.06. The mean MMAS-8 for each child ranged from 6.0 to 7.12.

Low immunization rates and high chemoprophylaxis coverage among participants

A low percentage of screened participants had complete, or any, immunization coverage based on for PCV-13 and Hib. Complete coverage for PCV-13 was 13.2% (43 of 325), with coverage of 12.9%, 1.2%, and 0.3% for the 1st, 2nd, and 3rd doses, respectively. Partial coverage for Hib was 37.5%, 35.4%, and 32.6% for the 1st, 2nd, and 3rd doses, respectively. Complete coverage for Hib was 32.3% (105 of 325). A total of 8.0% (26 of 325) of those screened had not received any routine immunizations.

In contrast, a majority of participants had received chemoprophylaxis including anti-malarial medications and penicillin V. The coverage for anti-malarial prophylaxis with daily oral proguanil was 99.1% (321 of 325), and pneumococcal prophylaxis with daily oral penicillin V was 78.5% (255 of 325).

Early results indicate that moderate fixed-dose hydroxyurea therapy is safe

Serious adverse events and adverse events occurred with similar rates in both the treatment and comparison group, Table II. A total of 12 deaths occurred: 2 deaths in the treatment group (2.69 per 100 patient-years based on intention-to-treat analysis) and 10 deaths in the comparison group (1.81 per 100 patient-years) (p = 0.67). The first participant in the treatment group that died was on hydroxyurea therapy for 18 months with a dose of 23.5 mg/kg/day. He was hospitalized for infection with severe anemia, subsequently developed seizures, and was treated with broad-spectrum antibiotics, antimalarial therapy, and exchange transfusion. The second participant, initially in the treatment group, developed progressive renal disease of unknown etiology with an initial creatinine of 112 μmol/L. The creatinine level gradually increased to > 200 μmol/L until visit 17, when he was withdrawn from the study, and hydroxyurea was continued on compassionate basis to decrease the

likelihood of acute vaso-occlusive events. The second participant died one month after being administratively withdrawn from the trial. Of the participants who died, none received PCV-13 vaccinations and only two were vaccinated against Hib. At the time of death, all participants were prescribed malarial prophylaxis, and 10 of 12 participants were prescribed penicillin prophylaxis, Table III. One stroke occurred in a participant in the comparison group, with TCD measurement of 183 cm/s in the right MCA and 116 cm/s in the left MCA ten months prior to the stroke.

Overall, no laboratory evidence of severe myelosuppression was recorded in any of the participants during the monthly laboratory assessments. Out of 712 complete blood cell counts, the number of times when platelet count $< 80 \times 10^9$/L and absolute neutrophil count $< 1.0 \times 10^9$/L was two and four, respectively; and neither of the values were persistently low after a repeat evaluation with no dose adjustment. Approximately 4.6% (33 of 712) of all hemoglobin measurements were < 6 g/dL. Only two children had at least two consecutive hemoglobin levels of < 6 g/dL: one with progressive renal failure and ultimately died because of renal failure and the second child with chronic hypersplenism.

DISCUSSION

Strokes in children with SCA result in immeasurable suffering, disability, and premature death.[20] Despite the majority of children with SCA being born in Africa [3, 4] and the evidence that interventions are available to help prevent strokes,[6, 21] no systematic attempt has been undertaken to prevent strokes in this continent. To address this large gap in medical knowledge and humanitarian need, we designed and implemented the SPIN (Stroke Prevention in Nigeria) trial.

Completion of the SPIN Trial had three important findings. First, our results demonstrated that parents of children with SCA in Nigeria have at least similar, if not higher, rates of successful recruitment, retention, and adherence to study medication when compared to comparable trials in high-income countries.[22–24] Second, we provided evidence that creating SCA Stroke Prevention Teams, consisting of a skilled TCD sonographer, pediatrician, and nurse, is feasible in Africa. Third, we demonstrated that for children with SCA living in Africa, in the absence of a completed randomized controlled clinical trial (RCT) for primary stroke prevention, moderate fixed-dose hydroxyurea therapy (~20 mg/kg/day) is a reasonable strategy to undertake with monthly clinical and laboratory surveillance.

In Africa, shortages of TCD machines and health care providers with the requisite skills to perform TCD testing (such as radiologists) are major barriers to implementing routine TCD examinations. Obtaining accurate TCD measurements with certified ultrasonographers, who were not radiologist, was the rate-limiting step for our trial. To our knowledge, this is the first effort to establish a TCD training program in non-radiology physicians in Africa. Local practices at our study sites in Nigeria, prevented non-physicians from learning TCD techniques. Our TCD training approach was successful with the inter-observer variability coefficient > 0.8 among all trainees. Ultimately, when primary stroke prevention becomes a priority in Africa, radiologists will be needed to certify the number of non-physician ultrasonographers.

Previous studies demonstrated intra- and inter-observer variability were important sources of measurement error in TCD assessments.[25, 26] In addition to observer variability, poorly defined participant TCD variability (or intra-participant standard deviation) must be considered when interpreting TCD measurements. In children with SCA with two TCD measurements evaluated less than 6 months apart, the 95% confidence limit for change in steady state TCD measurement was 29 cm/s.[27] In the recently completed TCD with Transfusion Changing to Hydroxyurea (TWITCH) trial, for children receiving blood transfusion therapy with at least 6 measurements, the average within participant variation was between 10.2–12.3 cm/s.[28] To minimize the contribution of participant TCD variability in assessment of intra-observer variability of the skilled radiologist (trainer), we elected for the trainer to repeat the TCD measurement in the same participant within a 3-hour time window. The results demonstrated that even in the best of circumstances, there will be a 7–12% variability in the assessment of TCD when performed by a skilled radiologist in the same child on the same day. Together, these data validate our approach of utilizing entry criteria of two independent TCD values   200 cm/s or one value > 220 cm/s, preferably performed by a second certified ultrasonographer.

Prior to starting the trial, we were uncertain of the appropriate hydroxyurea treatment dose (fixed-dose ~10 mg/kg (low), fixed-dose ~20 mg/kg (moderate), or maximum tolerated dose). However, based on the hydroxycarbamide in very young children with sickle-cell anaemia trial (BABY HUG) where participants were randomly allocated to moderate dose hydroxyurea therapy or placebo, [29] a moderate dose of hydroxyurea is not associated with rates of increased cytopenias. The rate of significant cytopenia (absolute neutrophil count < 1.5 x10^9/L, platelets < 150×10^9/L, reticulocytes < 80,000/μl, unless hemoglobin is > 9 g/dL) is no different than in children not on hydroxyurea.[29] Further, approximately 80% of the children in the trial dropped their TCD measurements to < 200 cm/s, approximately three months after starting hydroxyurea therapy.[30, 31] In comparison, among participants in the Optimizing Primary Stroke Prevention in Sickle Cell Anemia (STOP 2) trial, after initiating of blood transfusion therapy, 52% of the participants had normal TCD measurements after a mean of 4.3 months.[32] These data, coupled with those from the recently completed TWiTCH Trial demonstrating that hydroxyurea therapy was non-inferior to blood transfusion for primary stroke prevention in children with abnormal TCD measurements, after a year of regular blood transfusion therapy,[6] strongly suggest moderate dose hydroxyurea therapy is a reasonable starting point for primary stroke prevention in Africa.

The vaccination rate was lower than anticipated. The inadequate PCV-13 and Hib vaccination coverage is most likely due to the considerable out-of-pocket expenses for those vaccines for families rather than any lack of counseling on the importance of receiving the vaccines. The median annual family income of $5490. The out-of-pocket cost for the one PCV-13 vaccination is $60 in Kano, Nigeria. Given the increased risk of infection and observed mortality rate in children with SCA, we believe expanding efforts to treat African children with SCA with hydroxyurea therapy should be coupled with efforts to ensure complete vaccination coverage, at least against *S. pneumoniae* and *H. influenzae*.

As anticipated, the feasibility trial has inherent limitations. First, a median follow-up duration of just over two years does not fully address the concerns about retention for the

phase III trial (planned therapy for a minimum of least three years), long-term toxicity of hydroxyurea, or whether hydroxyurea therapy has a durable impact on preventing strokes in children with abnormal TCD measurements. The third year was planned as a transition year between the initial R21 funding and receipt of funding for a phase III randomized controlled trial. As a result of funding from the National Institute of Neurological Disorders and Stroke (1R01NS094041), we will follow the participants in the current feasibility trial for a mean duration of 6 years. Additionally, with the new funding, the teams will conduct a RCT comparing moderate fixed-dose hydroxyurea therapy (~20 mg/kg/day) to low fixed-dose hydroxyurea (~10 mg/kg/day) therapy for primary stroke prevention in children with SCA. Second, the initial interval between obtaining the laboratory values and reviewing them in a timely fashion was less than optimal. To address the challenge, we recruited laboratory personnel allocated to the trial. We also instituted weekly reviews between the study site and coordinating center teams that included a local study monitor whose sole responsibility was to review all laboratory values and follow the safety algorithm. Finally, 10 of 12 reported deaths in the combined treatment and comparison groups occurred at home, with no further examinations performed to determine the cause of death—an intrinsic limitation in attributing cause of death in low- and middle-income countries.[33] In addition to these limitations, challenges relevant to adhering to regulatory guidelines, study medication, and evaluations were described in detail elsewhere.[34]

Results of our first ever NIH-funded SCA stroke prevention feasibility trial in Africa indicate that parents of Nigerian children with SCA are willing to participate in a clinical trial and adhere to hydroxyurea therapy to prevent strokes. We have provided preliminary evidence a moderate fixed-dose hydroxyurea therapy (~20 mg/kg/day) is well-tolerated and may have efficacy in preventing strokes in children with SCA. We have established a practical SCA-specific hydroxyurea safety-monitoring algorithm for children with SCA living in Africa. Until the phase III trial is completed in Africa (NCT02560935), we recommend formation of SCA stroke prevention teams consisting of a certified TCD ultrasonographer, pediatrician, and a nurse, for initiating a moderate fixed-dose of hydroxyurea therapy, coupled with monthly laboratory and clinical surveillance.

Acknowledgments

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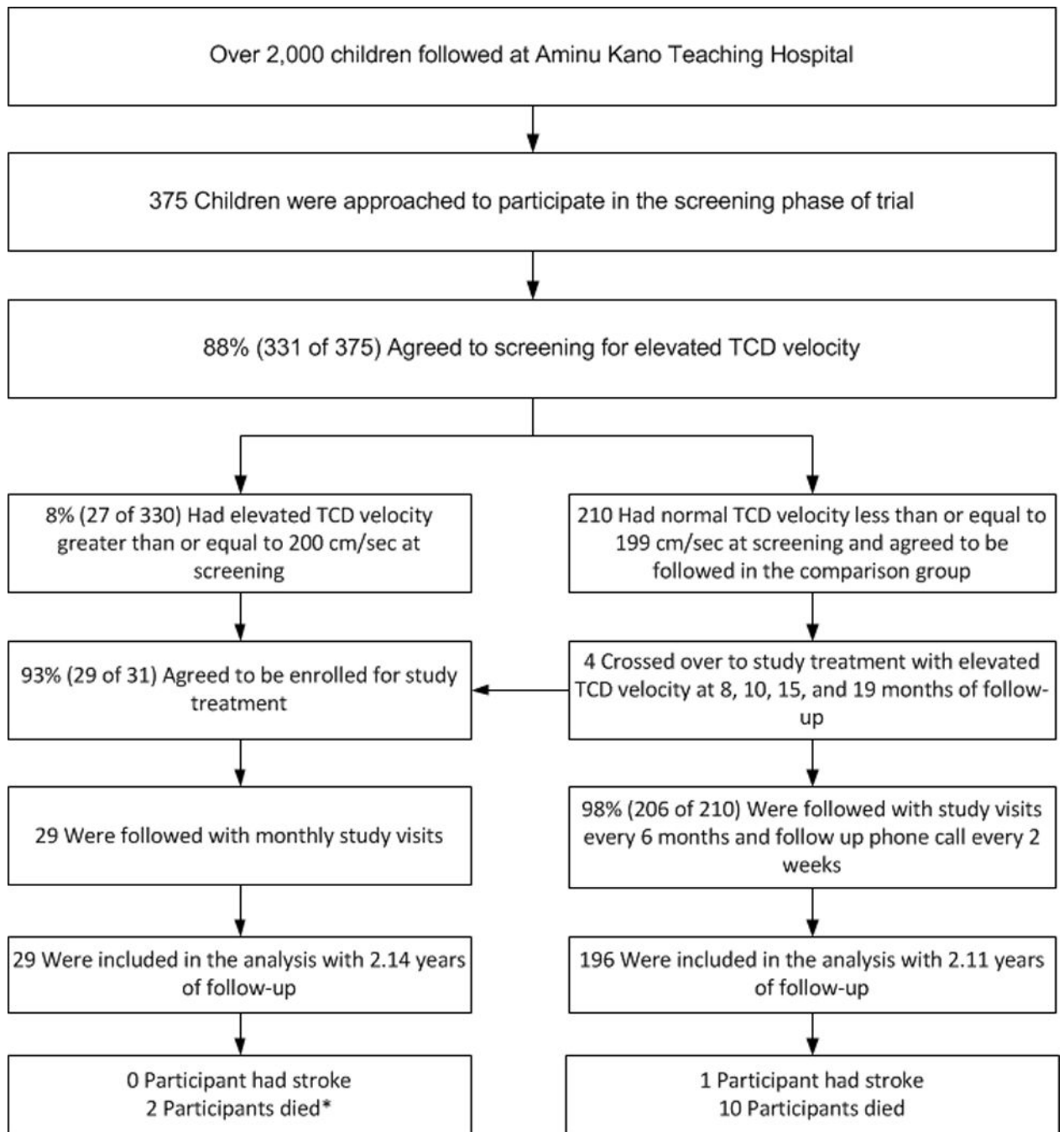
Figure 1.
SPIN Trial Participants Recruitment Flow Diagram

Table I

Baseline demographics and characteristics of all children with sickle cell anemia enrolled in in SPIN Trial

Demographics:	Treatment N = 29[¥]	Comparison N = 206	P value
Age (years), median (IQR)	6.8 (5.7,9.2)	8.2 (6.3,10.4)	0.053
Gender (Female), %	52	52	0.94
Height (cm), median (IQR)	123.0 (114.0, 134.0)	125.5(115.2, 132)	0.47
Weight (kg), median (IQR)	20.0 (17.0,23.0)	20 (17.0,24.0)	0.60
Ethnicity (Hausa/Fulani), %	81.5	91.8	0.17
Tertiary education for parent (college/university training), %	48	79	0.001
Length of follow-up (years), median (IQR)	2.1 (1.8,2.7)	2.1 (1.9,2.5)	0.44
Annual income[±]			
<$5000	48%	36%	
>=$5000	52%	64%	0.24
Mean	4183	5395	
Median	4270	6100	
Hydroxyurea dose (mg/kg/day), minimum and maximum dose	19.23 (16.58, 21.88)	none	

[±]United States Dollar

[¥]Includes crossovers from the comparison group to the therapy group

Table II

Comparison of incidence rates of hospitalization in the first 36 months between the treatment and comparison groups in the SPIN trial

Indication for hospitalization	Treatment Group (Per 100 person-years)	Comparison Group (Per 100 person-years)
Acute chest syndrome	0	0.54
Osteomyelitis	0	0.54
Infection	6.73	2.18
Pain	12.12	21.22
Stroke	0	0.18
Transfusion	8.08	3.63
Malaria positive WHO*	9.42	12.15
Fever	12.12	7.07
Other	8.08	2.53
Total	56.54	**50.24**

*World Health Organization

Table III

Age, immunization status, chemoprophylaxis status and suspected causes of death among SPIN Trial participants. No autopsies were performed, and cause of death was based on local pediatrician's impression after review of the medical records

Subject Number	Age at Death (Years)	Influenza Type 1 Vaccine	Pneumococcal Vaccine	Penicillin V	Palludrine	Postulated cause of death
			Comparison Group			
1	12	YES	NO	YES	YES	Severe anemia
2	7	YES	NO	YES	YES	Transfusion reaction
3	8	NO	NO	YES	YES	Malaria
4	6	NO	NO	YES	YES	Severe anemia
5	10	NO	YES	YES	YES	Septicemia
6	12	YES	NO	NO	YES	Severe anemia
7	5	NO	NO	YES	YES	Malaria
8	11	YES	NO	YES	YES	Malaria
9	10	YES	NO	YES	YES	Severe VOC
10	8	NO	NO	YES	YES	Severe VOC
			Treatment Group			
1	7	NO	YES	YES	YES	Septicemia and severe anemia
2	10	NO	NO	YES	YES	Renal disease