Published in final edited form as:
Pediatr Blood Cancer. 2010 February ; 54(2): 256–259. doi:10.1002/pbc.22282.

Transcranial Doppler Ultrasonography (TCD) in Infants with Sickle Cell Anemia: Baseline Data from the BABY HUG Trial

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Abstract

Background—Transcranial Doppler ultrasonography (TCD) is used to predict stroke risk in children with sickle cell anemia (SCA), but has not been adequately studied in children under age 2 years.

Procedure—TCD was performed on infants with SCA enrolled in the BABY HUG trial. Subjects were 7–17 months of age (mean 12.6 months). TCD examinations were successfully performed in 94% of subjects (n=192).

Results—No patient had an abnormal TCD as defined in the older child (time averaged maximum mean velocity ≥ 200cm/sec) and only 4 subjects (2%) had velocities in the conditional range (170–199cm/sec). TCD velocities were inversely related to hemoglobin concentration and directly related to increasing age.

Conclusion—Determination of whether the TCD values in this very young cohort of infants with SCA can be used to predict stroke risk later in childhood will require analysis of exit TCD's and long-term follow-up, which is ongoing. (ClinicalTrials.gov number, NCT00006400)

Keywords

Transcranial Doppler Ultrasonography; TCD; sickle cell anemia; stroke; infant

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Introduction

Transcranial Doppler ultrasound (TCD) is used in children with sickle cell anemia (SCA) to detect increased risk of arterial ischemic stroke (AIS) [1,2]. Adams et al. reported a high risk of AIS in children with a TCD velocity ≥ 200 cm/sec, but this risk was determined in older children [1,2].Based on this work and the subsequent STOP trial [2], TCD screening is employed in children 2–16 years of age; its use in infants <2 year of age is not established. As peak AIS risk in SCA occurs at approximately age 4 years [3,4] and since cerebral blood flow (CBF) and velocity are age dependent, it is unclear whether the same cut-off for abnormal TCD velocity is pertinent to younger children [2].

BABY HUG is an NHLBI-NICHD sponsored Phase III double-blinded clinical trial in infants with SCA comparing hydroxyurea (HU) to placebo to ascertain the efficacy of HU in preventing damage to the spleen and kidneys (NCT00006400). As a secondary endpoint in this trial, TCD was performed to determine possible effects of HU on the brain. Here we review the baseline TCD data obtained during pre-randomization screening of infants enrolled in BABY HUG.

Methods

Infants with SCA evaluated at baseline for the BABY HUG study are reported. There were 87 males and 112 females. Infants were 7–17 months of age (mean 12.6 months) during screening, had no history of stroke and were not receiving chronic blood transfusions. Subjects had HbSS (n=191), or HbSβ^0 thalassemia (5). Hemoglobin diagnoses from 3 subjects were not available. The infants underwent TCD examination using the Nicolet Companion (EME) 2-MHZ pulsed Doppler instrument, the Bayley Scales of Infant Development II examination, and blood collection (including CBC, reticulocyte count, chemistry panel and fetal hemoglobin quantification). In addition, a brain magnetic resonance imaging (MRI) and magnetic resonance angiography (MRA) were obtained in a small subset [5]. Blood flow velocities were recorded using the Stroke Prevention Trial in Sickle Cell Anemia (STOP) protocol with the exception of reducing the standard sample volume to 4 mm because this improves TCD data in the smaller child [2]. No sedation was used and all children were awake during the examination. The time averaged maximum mean velocity (TAMM) was measured in seven arteries on both sides to categorize the study as either normal (all recordings <170 cm/sec), conditional (any recording 170 – 199 cm/sec) or abnormal (any recording ≥200 cm/sec). Recordings from both middle cerebral (MCA) and internal carotid (distal portion or bifurcation) (ICA) arteries were required for a TCD exam to be considered adequate. Participation in BABY HUG required at least an attempted TCD exam.

TCD examinations were performed by a traveling examiner from the reading center at the Medical College of Georgia (MCG) or by a local BABY HUG certified examiner, if available. The exams were read by blinded reviewers at MCG and results transmitted to the Coordinating Center (C-TASC) for statistical analysis.

The distributions of the TCD velocity, hemoglobin (Hb), HbF, absolute reticulocyte count (ARC), and score on the Bayley mental scale development index (MDI) were checked. A square root transformation was applied to the ARC variable. Five simple linear regression models were constructed with TCD velocity as a dependent variable. Age, Hb, HbF, ARC, and MDI were respectively included in the model as independent variables. A multiple linear regression model was constructed. Model selection methods including forward selection, backward selection, and stepwise selection yielded the same final model. The interaction terms were tested and none of them were significant. ANOVA was performed to

test TCD velocity differences across age groups. Tukey's method of pair-wise comparisons was used to analyze age. SAS Version 8.2 (SAS Institute, Cary NC) was used to produce the descriptive statistics and perform regression analyses.

Results

TCD examinations were attempted on 199 infants. One (0.5%) was unsuccessful (no data obtained) because of the subjects' lack of cooperation and six (3%) were inadequate. Of the remaining 192 TCD exams, 188 were normal and four had at least one conditional velocity. No subjects were ineligible for the BABY HUG study due to abnormal TCD result.

The average left MCA TAMM velocity was 116.3 ± 22.0 cm/sec and that of the right MCA was 114.3 ± 22.3 cm/sec. Ten percent of subjects had TAMM velocities ≥ 149 cm/sec and 20% ≥141 cm/sec. The subjects were divided into four age groups and the MCA TAMM velocity of all vessels studied was determined for each group (Table I). ANOVA showed significant differences ($p<0.001$) among age groups for left TAMM, right TAMM, and overall TAMM. Tukey's method of pair-wise comparisons showed that there was a general increasing trend of TCD velocities with age.

Simple regression analyses showed significant associations between the highest TAMM velocity and the individual variables of interest except the Bayley MDI. There were positive and negative correlations of the highest TAMM velocities with age and Hb, respectively (Fig. 1A–C, Table II). The multiple regression model yielded significant associations between TCD velocities and age, total Hb (inverse association), and square root of the ARC when adjusted for the other variables (Table II). In this larger model, every one-month increase in age was associated with an average increase in the highest TAMM of 2.0 cm/sec with a 95% confidence interval (C.I.) of 1.0–3.1 ($p<0.001$). Furthermore, a 1 g/dL increase in Hb level was associated with a decrease in the highest TAMM of 3.8 cm/sec (95% C.I. −6.3 to −1.2, $p=0.005$) and a $1K/mm^3$ increase in square root of the absolute reticulocyte count was associated with an increase in the highestTAMM of 1.1 cm/sec (95% C.I. 0.2–1.9, $p=0.012$).

Discussion

Children with SCA generally have high TCD velocities in all cerebral blood vessels compared to age-matched controls [1,2,6,7,8], but there are few data available about velocities in infants with SCA less than 2 years of age. Hogan et al. reported that infants with SCA had MCA velocities of 50 – 112 cm/sec (median 70) at 3 months of age, 50–160 cm/sec (median 89) at 9 months of age and 51–120 cm/sec (median 97) at 12 months of age [9]. However, the sample size of this study was very small (n=14), TCD typically was recorded while the infant was sleeping, and there was no information provided about stroke.

Hogan et al. performed serial studies and did show an inverse relationship with developmental testing and TCD derived velocity as has been reported in older children with SCA [10]. We showed no correlation with cognitive testing and increasing velocity but Hogan et al. evaluated patients serially which might have made their correlations with the Bailey Infant Neurodevelopmental Screener more robust. It is possible that our study at exit will show a better correlation of TCD with cognitive function.

The BABY HUG study provides TCD data on the largest sample of infants with SCA to date, with adequate baseline TCD evaluations obtained on 192 subjects. All but four (2%) were normal by STOP criteria as compared to 9.3% abnormal and 17.6% conditional in STOP screening of children 2–16 years of age [2]. Baseline TCD velocities varied inversely with the hemoglobin level when adjusted for age as expected, and the direct association with

the reticulocyte count was anticipated because of the known inverse relationship between Hb level and reticulocyte count

The correlation of TCD velocity with increasing age is of particular interest. Velocities of the basal cerebral arteries have been found to be age dependent in healthy children with normal hemoglobin levels [1,11]. For example, the mean MCA velocity is low soon after birth (24 cm/sec) but increases rapidly during the first three months of life to 42 cm/sec, probably related in part to the physiologic anemia of infancy. Subsequently, the mean MCA velocity rises slowly to 74 ± 14 cm/sec at 3–12 months of age and 85 ± 10 cm/sec between the ages of one and three years. The highest values occur between the ages of four and six years with peak MCA velocity approaching 100 cm/sec [11]. After that, velocities decrease linearly (mean MCA velocity 80 cm/sec at 10–18 years of age). We found a similar developmental trend in infants with SCA. The average TAMM MCA velocity of 111 cm/s in infants with SCA is higher than in normal children without anemia but substantially lower than observed in the STOP trial (approximately 140 cm/sec), in which all patients were age 2 years or greater and there was no significant age effect over this older range [12].

Another factor that could affect TCD velocity is vascular stenosis [13]. In SCA the earliest onset of large vessel stenosis is not known. Wang et al previously reported MRA findings in a baseline subset of very young children with SCA from the BABY HUG study [5], and MRA showed no occlusion or significant stenosis in any patient. The trend of increasing velocity with age observed in our study is more likely related to anemia and developmental demands for increased blood flow, not unlike what is seen in normal children, although our subjects had higher velocities overall.

In the same study, 3 children who underwent MRI had silent infarcts (13%; 3 out of 23 MRI performed) [5]. The silent infarct group had velocity asymmetries not found in the non-silent infarct group but the numbers are small and conclusions difficult to derive [5].

Cerebral blood flow (CBF) elevation and age may be independent risk factors for AIS in SCA, independent of vasculopathy [13]; therefore, the absolute TCD velocity that predicts AIS in the one year-old may be different than in the four year-old. Our categorization of TCD values as normal, conditional or abnormal based on the STOP trial results is, in the present study, arbitrary, although based on established norms in older SCA children. Different norms for this younger age group may be necessary if one year-olds truly have “abnormal” velocities that are predictive of stroke. Data obtained from TCD exams of subjects when they exit the BABY HUG study (following two years of HU or placebo) will help determine if our subjects’ baseline velocities within the normal to conditional range (by STOP criteria), will yield predictive information on the risks for developing markedly high velocities, vasculopathy and later stroke.

Acknowledgments

We acknowledge the efforts of the BABY HUG subjects and their families, the contributions of all who participated in BABY HUG (http://www.c-tasc.com/cms/StudySites/babyhug.htm) and the support of the National Heart, Lung and Blood Institute/National Institutes of Health Contracts N01-HB-07150 to N01-HB-07160, with additional support from the Best Pharmaceuticals for Children Act and the National Institute of Child Health and Human Development.

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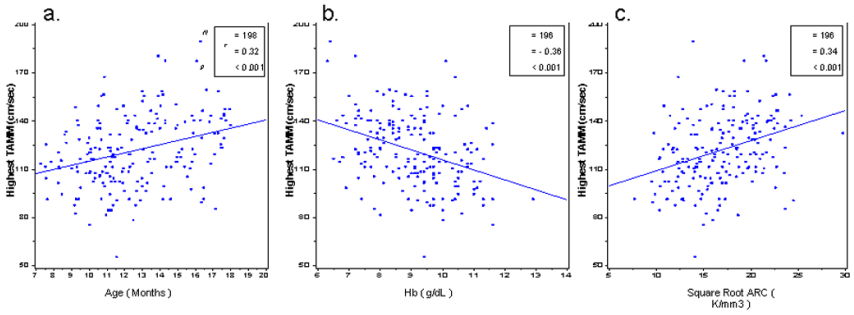

Figure 1.

Highest Time averaged mean maximum velocity (TAMM) vs. Age, Hemoglobin (Hb), and Absolute Reticulocyte Count (ARC) Expressed as the square Root of the Value.

Table I

TCD Highest TAMM (Time averaged mean maximum velocity) (cm/sec) by Age

Age Group (Months)	Left Maximum*			Right Maximum**			Overall Maximum^		
	N	Mean (SD)	Range	N	Mean (SD)	Range	N	Mean (SD)	Range
7 – 10	32	108.3 (16.5)	77–141	32	108.6 (17.8)	74–149	33	114.4 (16.1)	83–149
10 – 13	78	109.5 (20.6)	56–168	82	109.0 (21.0)	51–157	82	115.4 (20.6)	56–168
13 – 16	54	122.4 (20.6)	82–178	54	119.4 (23.5)	83–181	54	129.0 (21.1)	92–181
≥ 16	29	131.6 (23.2)	86–190	29	126.3 (22.4)	83–160	29	134.8 (23.6)	86–190
Total	193	116.3 (22.0)	56–190	197	114.3 (22.3)	51–181	198	121.8 (21.9)	56–190

* Maximum velocity for the seven left-sided vessels

** Maximum velocity for the seven right-sided vessels

^ Maximum velocity for all fourteen vessels.

Table II

Regression Analyses of TCD Highest Time averaged mean maximum velocity (cm/sec) Versus Other Variables

Model	Variable	N	Estimate*	95% Confidence Interval	P
Simple Regression	Age	198	2.5	1.5 – 3.6	<0.001
	Hb	196	−6.2	−8.5 — −3.9	<0.001
	HbF	193	−0.8	−1.2 — −0.5	<0.001
	ARC**	196	1.9	1.2 – 2.6	<0.001
	Bayley MDI***	195	−0.2	−0.5 — 0.1	0.189
Multiple Regression	Age	193	2.0	1.0 – 3.1	<0.001
	Hb	193	−3.8	−6.3 — −1.2	0.005
	ARC**	193	1.1	0.2 – 1.9	0.012

* Estimate of the regression coefficient in the simple or multiple regression model

** ARC = Absolute Reticulocyte Count expressed as the square root of the value

*** MDI= Mental Developmental Index