Toward a Stroke-Free Childhood in Sickle Cell Disease

The 2013 Sherman Lecture

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Stroke in childhood is not common outside of congenital heart disease and a few other conditions including sickle cell disease (SCD). The background rates reported have been between 2.3 and 2.7 per 100,000 per year.1–3 Adults, on the contrary, have a background rate of ≈800 per 100,000.4 There are some special conditions that increase the risk including congenital heart disease, trauma, infections (basilar meningitis), cancer, and SCD.5

Stroke rates in SCD were estimated to be high at 500 to 1000 per 100,000.6 The Baltimore Washington Cooperative Young Stroke Study reported data from 1988 to 1991 at a rate of 285 per 100,000 children for SCD.7 For children with SCD, this is a long way for a stroke-free childhood.

SCD fundamental pathophysiology results from hemoglobin S forming polymer strands inside the red blood cell which causes distortion of the red blood cell, leading to microcirculatory occlusion and accelerated erythrocyte destruction with release of toxic-free hemoglobin into the vascular system. How SCD leads to cerebrovascular disease is only partly understood. Although there are many manifestations of vascular pathology in SCD, the one that plays the most prominent role is an intracranial cerebral large artery vasculopathy causing stenosis or occlusion. This unusual vascular disease process was confirmed 90 years ago8 as a cause of large brain infarctions in patients with SCD, typically children, and confirmed with arterial studies much later.

In the mid-1980s, a confluence of factors, from disparate worlds, led to the work herein described. Aaslid et al introduced the transcranial Doppler (TCD) for detection of intracranial artery vasospasm in 1982 based on experience in Norway.9 Interest in this tool was first manifested in neurosurgery but soon its potential as a noninvasive way to assess intracranial arteries became apparent and attracted the interest of neurologists (Figure 1). In the hematology world, regular blood transfusions had been adopted by hematologists to prevent recurrent stroke in SCD.10 In Augusta, GA, the pediatric hematologists at Medical College of Georgia were vexed by stroke in these children and asked neurologists for help.

Although there was no clinical trial, the reduction in second and subsequent stroke seemed to be substantial among those children placed on regular blood transfusion.11 But the problem with starting transfusion after stroke is that, by definition, some degree of brain damage has already taken place. This could largely be averted by transfusing all children with SCD but this would be a hard strategy to implement because the stroke rate in SCD, although much higher than the background rate for children without SCD, is still only in the range of 0.5% to 1.0% per year. Somewhere between 100 and 200 children would need to be transfused to prevent 1 stroke a year; side effects and cost would be prohibitive.

Clearly, a primary prevention strategy would hinge on a practical way to select those who needed transfusion the most. This project began in earnest in 1986, and it was necessary to first develop velocity standards for normal kids,15 obtain experience with the TCD in children with SCD,13 measure the baseline velocity elevation from anemia itself, correlate TCD with angiography,14 and prospectively validate TCD as a predictor of risk for stroke with long-term clinical follow-up of children at risk.

From 1988 to 1992, a single-center prospective study was instrumental in validating TCD as a predictor of risk. Rather than doing cross-sectional studies correlating TCD to imaging studies, the results of which would be of marginal significance because MRI or any other test, including catheter angiography, had not been evaluated as a prospective risk predictor, a long-term prospective study of 315 children with no history of stroke was undertaken. Children aged 3 to 18 years were enrolled and received TCD but no intervention. The resulting publications15,16 reported this observational study during which 17 incident strokes were documented. Children aged 3 to 18 years were enrolled and received TCD but no intervention. The strong relationship between TCD measured velocities and stroke.

Stroke risk increased dramatically with time averaged mean velocity in the internal carotid or middle cerebral arteries, and although there was no biological cut point, the report identified 170 cm/s as a possible risk cut point. This velocity was 1.5 SD above the mean. Other secondary exploratory findings were as follows:

1. If highest velocity (Vmax) was ≥200 cm/s, 40% had stroke within 30 months.
2. The latency to stroke, however, was highly variable from 1 to 40 months, but with higher the Vmax there was a trend toward more proximate stroke risk (5 children with velocity ≥240 cm/s had stroke in <9 months after the TCD showing this high velocity was recorded).

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Because there was no complete and regular surveillance, it was not possible to pinpoint precisely in most cases the change from low- to high-risk TCD.

In retrospect, we had not set out to find a treatment but only a predictor. But having found what seemed to be a strong predictor, it was important, as stroke neurologists, to provide guidance to the hematologists taking care of these patients. Because regular blood transfusion was being used to prevent second and subsequent stroke, and although there had been no clinical trial, the data from Powars et al\textsuperscript{11} indicated that stroke rates were cut dramatically.

There were several important decisions to be made in planning for a randomized clinical trial.\textsuperscript{17} In most situations, equipoise revolves around whether the treatment works with acceptable toxicity. In this case, the equipoise that informed the trial was more the question of whether TCD, applied in a multicenter fashion, would work. The decision was made to offer the study to any child with SCD who had no history of overt stroke (an accepted indication for regular transfusion) and to defer the MRI until after randomization. It was expected that the MRI might show in many cases some evidence of ischemic damage and that some clinicians might react by choosing empirical therapy with transfusion rather than enroll the patients in a clinical trial. This decision was vindicated when subsequent studies showed some increase in risk of overt stroke when MRI was abnormal, but no clear indication for transfusion on the basis of MRI alone has yet emerged in the 20 years since the design of the Stroke Prevention Trial in Sickle Cell Anemia (STOP) trial (but the Silent Infarct Transfusion study\textsuperscript{18} may alter that when completed).

Another key trial design question was the velocity cut point. Neither did the prospective study from the Medical College of Georgia identify a specific cut point nor did the data suggest that there was any sort of inflection point where risk increased in a nonlinear fashion. Cut point selection is a classic sensitivity/specificity balancing act. The decision was made to require 2 TCDs that reached or exceeded 200 cm/s using the time averaged mean of the maximum, the velocity endorsed by Aaslid et al\textsuperscript{10} in their initial TCD article. The velocities of 170 cm/s was used to define low risk, and in between subjects received greater frequency of TCD but were not randomized.

Sample size calculations assumed that transfusion would be highly effective. Projecting a 70% reduction in stroke over 24 months called for a total sample of 130 patients, an extremely small sample for a stroke prevention trial. Accordingly, the success of the trial depended in fact on 1 issue: could the TCD screening process that was so successful in the single-center study be replicated across multiple sites and would this select a high-risk population? To avoid trying to use sham transfusion, adjudication was performed by a blinded panel of pediatric neurologists looking over all the available information after any mention of treatment had been redacted. Trial design and results are shown in Figure 2A and 2B.

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{tcd.png}
\caption{Illustration of transcranial Doppler (TCD) examination showing probe placement to measure middle cerebral artery and internal carotid artery.}
\end{figure}
Screening began in 1995 and went on for 18 months. In September of 1997, 16 months early, the Data and Safety Monitoring Board closed the study because of an imbalance in the strokes, 11 (10 on study) in the standard care arm and 1 in the treatment arm (Figure 2B). A clinical alert was sent to 5000 physicians in the United States by National Heart, Lung, and Blood Institute. For the next 2 months, all families were brought into their respective clinics, the trial results explained, and a decision on open-label treatment was made. Most of those on transfusion (75%) stayed on transfusion, and many of those still in the standard arm at the time of trial closure (55%) elected to switch to transfusion.19,20

The study was designed to determine whether transfusion prevented stroke but could not provide guidance on how long it had to be continued to achieve sustained benefit. At the time, there were theories that the vasculopathy seen in these children might be triggered by infection or might be a product of the naturally high cerebral blood flow demands of early childhood. If so, perhaps a limited intervention would interrupt the process and allow transfusion to be withdrawn. The second STOP study was called Optimizing Primary Stroke Prevention in Children with Sickle Cell Anemia: STOP II and was conducted from 2000 to 2004. Key design features and the results are shown in Figure 3A and 3B.

This study was halted prematurely but for a different reason than the STOP study. In this case, the standard arm was continued transfusion, and the experimental arm was withdrawal of transfusion. All 16 end points were in the experimental arm. Technically all were TCD end points in that the first indication of risk was the re-emergence of abnormal TCD, but there were 2 children who had stroke before the second confirmatory TCD (as per protocol) could be performed.

Several others had been crossed over from no transfusion back to transfusion because of pain or reasons than stroke or reversion to high-risk TCD. Clearly this strategy did not work, and the resulting recommendations from National Heart, Lung, and Blood Institute were to continue transfusion indefinitely until further research could identify safe alternatives.

Since that time 2 alternative treatment studies have been undertaken. The first was Stroke With Transfusions Changing to Hydroxyurea (SWITCH) that randomized children with prior stroke on regular blood transfusion to continue or be transitioned to hydroxyurea treatment. The study was halted when 7 strokes were observed in the hydroxyurea arm and none in the continued transfusion arm. Analysis of the arterial imaging showed that those with stroke had advanced cerebrovascular disease.22 A new approach was taken with TWiTCH (Transcranial Doppler With Transfusions Changing...
to Hydroxyurea), the follow on study; the subjects were children placed on prophylactic transfusion for abnormal TCD and no clinical evidence of stroke. In this study, the extra step was taken to select those with advanced arterial disease and to convert to hydroxyurea more gradually than in SWITCH. The study has completed enrollment and is in progress.23

It has been >15 years since the first STOP clinical alert. Is there evidence that this approach is making a difference? An early report by Fullerton et al23 from California suggested a drop in hospitalizations from first stroke after STOP but these data were only suggestive. However, in the past 10 years, 3 large clinics, 2 in the United States and 1 in France, reported dramatic drops in first stroke after implementation of the TCD screening and intervention to prevent stroke.24–26

There followed 2 reports using the National Inpatient Sample and a similar approach but slightly different time periods, both of which reported a large drop in the fraction of pediatric stroke hospitalizations because of SCD after STOP compared with the pre-STOP era. Ovbiagele and Adams27 examined data from hospitalized patients with stroke comparing 1997 and 2006 looking at time trends related to stroke and SCD. Pediatric strokes with comorbid SCD represented 8.7% of the 1997 (pre-STOP) sample but only 4.8% in 2006 ($P=0.04$). In contrast, adult stroke patients with SCD were 0.3% of all hospitalized stroke in 1997 versus 0.5% in 2006 ($P=0.01$).27 George et al28 reported that “for those aged 5–14 years, the rate of ischemic stroke hospitalizations decreased by more than one half from 1995–1996 to 2007–2008 (from 27.8 to 13.6% $P<0.001$ . . .).” Finally and recently, an impact on death from ischemic stroke, likely attributable to implementation of the STOP protocol, was recently reported by Lehman and Fullerton.29 They evaluated the demographics and secular trends of mortality attributable to ischemic and hemorrhagic stroke in the United States to determine whether there was a decrease in the black–white disparity since the publication of the STOP study in 1998. They used US death certificate data from 1988 to 2007. During this period the black–white disparity of ischemic stroke mortality dropped from 1.74 to 1.27, whereas there was no comparable decrease for hemorrhagic stroke. This is consistent with the cause of this decrease being the implementation of STOP which has been shown to impact ischemic stroke but not hemorrhagic stroke in children with SCD and which is the only change in management introduced in this period.29

Is this a stroke-free childhood? Not really, not yet, but it is a good start. Identification of high risk is clearly a big part of the solution as it allows targeted intervention. Although TCD is far from perfect, it does identify many of those at high risk for stroke. 

Figure 3. A and B, Optimizing Primary Stroke Prevention in Sickle Cell Anemia (STOP 2) trial design and results (Adams and Brambilla21). NIH indicates National Institutes of Health; SCD, sickle cell disease; and TCD, transcranial Doppler.
risk, facilitating intervention and the reductions seen during the past 15 years. Wider application of the protocol and effective interventions with agents less intensive than transfusion should widen the impact and make childhood even safer for the children of the world who have SCD.

Dedication

This article is dedicated to David Sherman, a dedicated father to his four children.

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References


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