

## Preventing Stroke in Sickle Cell Disease: 2021. The Role of Transcranial Doppler Ultrasound (TCD) When the Use of Transfusion is Problematic

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In 2009, as an invited Commentary to the article: “STOP” ing the Harm: When is State Intervention Justified? [1], I wrote that while TCD is an indicator of risk, not a biopsy diagnosis (such as proof of cancer), at some point in the velocity spectrum the high velocity detected by TCD reaches what many—myself included— believe is an unacceptable risk of stroke [2]. Even at the low end of the intervention window, 200 cm/sec Time Averaged Mean of the Maximum (TAMM), the point where periodic transfusion is recommended based on the STOP Trial [3], the risk is at least 10 times background and it goes up from there. The risk is markedly attenuated (>90%) by transfusion. Stroke by its nature is permanent. While some strokes are minor and survival with recovery is the expected outcome, it is not assured.

Since 2009 TCD has become more common and remains universally recommended. Unfortunately, we have not learned when the stroke “event” is to be precisely expected. In some cases, it can be very soon after the TCD reveals the high velocity. In the STOP [3] and STOP II [4] clinical trials, six strokes were observed in the protocol directed 4-week period between the first observed abnormal study and the planned “confirmatory” second TCD. In other cases, high velocity was observed without clinical event over many months while transfusion was being considered or had been declined. But it is clear from this experience that a high TCD is a ticking time bomb with a fuse of unknown length. Modern practice today is to initiate transfusion immediately if the TCD is >220 cm/sec although some (myself included) do not recommend waiting under any circumstance if the velocity is 200 cm/sec or greater unless there is concern about the study being a rare “false positive. Although there are a number of new testing methods that can determine perfusion deficits

and exhaustion of “vascular reserve”, these have not been validated to the point of incorporation into the standard protocol. In summary, the confidence we have that a high risk TCD is a valid marker of stroke risk is higher than it was in 2009 but we still do not know when to expect the stroke or whether we are treating a child who would, for whatever reason, never have a stroke without transfusion.

Despite these limitations TCD is strong evidence of impending harm [5]. As such it is not unreasonable to use as the basis to force parents to allow transfusion. Running a red traffic light does not always result in an accident but it is illegal because of the inherent risk. Society has long ago determined that there are situations where parents’ freedom to place their children at risk has legal limits. The conclusion I reached in 2009 remains relevant:

“So in the end the degree of risk really seems to be the dominant factor. What if the TCD is 300 cm/sec rather than 200 cm/sec, and MR testing shows existing brain and arterial damage? What if “harm” is already evident from poor school performance or clinically evident stroke? After a child with SCD has a clinical stroke, or the TCD rises to very high velocity and the MRI shows ischemic damage, the risk of significant further brain damage is higher still and may exceed 50% in the next few years. When the untreated prognosis gets bad enough, the case for legal intervention in my opinion grows stronger even before an “event” takes place. There is such a thing as “reckless endangerment” that operates legally even if a bad outcome is not yet evident” [2].

What is changing, however, are the preventive treatment options. There is abundant evidence that hydroxyurea (HU) treatment lowers TCD velocity and by extension, stroke

risk. There have been at least two randomized clinical trials, SWITCH [6] and TWITCH [7]. In SWITCH, hydroxyurea was tested as a replacement for chronic transfusion for secondary prevention after a stroke was documented. The trial was a clear failure and was prematurely stopped when there were 7 “breakthrough” strokes in the HU group as opposed to none in the “continue transfusion” group. All these patients had Magnetic Resonance Angiography (MRA) evidence of advanced arterial disease. On the other hand, in TWITCH, it was tested in the primary prevention setting and conversion to HU was not initiated until at least 12 months of transfusion had been given and the patient had been screened with MRA and found not to have advanced arterial vasculopathy. While the TWITCH protocol does involve a period of transfusion, there is growing evidence that, if started early enough, HU treatment may eliminate the need even for a limited period of transfusion by preventing the velocity from reaching the 200 cm/sec mark [8].

These new data have important implications for parents of children with SCD who object to transfusion. Instead of avoiding TCD for fear it will force the issue of treatment with forbidden blood products, parents should seek out TCD and ensure that their child gets TCD as early as possible and regularly throughout childhood. The BABY Hugs study proved that TCD can be accurately performed in young infants less than 2 years of age (where STOP Protocol screening is recommended to start) and even if less than ideal due to movement, experienced examiners have learned that these early studies increase the child’s comfort with TCD [9]. This means that with patience and persistence high quality studies should be routine by age 2, before vasculopathy has had a chance to become established. Early recognition of risk opens up the off label but reasonable prospect of HU treatment with aggressive TCD monitoring. This approach does not guarantee that transfusion won’t be needed but it should lower that risk. It is a very rational way to approach a situation where non-medical considerations make it highly desirable to avoid the issue of transfusion.

In addition to new studies with HU initiated in the so called “conditional” TCD range of 170-199 cm/sec, other treatments are now being tested that would have the same result (avoiding the transfusion trigger of 200 cm/sec) such as the HopeKids2 study. In this RCT voxelotor [10] is being compared to placebo in children with conditional TCD.

In fact, early and aggressive screening should be the norm for all children with SCD. As we demonstrated in the prolonged follow up phase of STOP, after the RCT was stopped, even with continued transfusion some children with advanced arterial disease at the time transfusion is started will eventually have stroke [11].

With all the evidence in hand, we should be able to have processes and programs in place to ensure that all children identified by newborn screening to have SCD get TCD early and often. Sadly, this is not the case. A lot more needs to be done.

But for those with special concerns about transfusion (eg religious objection), the best advice is somewhat counter intuitive:

Instead of avoiding TCD, make sure your child gets it early and regularly to identify stroke risk early and employ other treatments before transfusion becomes mandated.

## Disclosure

Author is a paid consultant for Global Blood Products.

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