Transcranial Doppler (TCD) screening for stroke prevention in sickle cell anemia: pitfalls in technique variation

**Abstract** Background. The Stroke Prevention Trial in Sickle Cell Anemia (STOP) identified children as being at high stroke risk if the time-averaged maximum mean velocity (TAMMV) of the middle cerebral or intracranial internal carotid arteries measured ≥200 cm/s. These values were obtained utilizing a 2-mHz dedicated nonimaging pulsed Doppler technique (TCD) and manual measurements. Questions have been raised as to the comparability of results obtained with different ultrasound machines and measurement techniques.

Objective. The purpose of this study was to compare nonimaging (TCD) and transcranial duplex imaging (TCDI) findings in children potentially at risk for stroke with sickle cell disease.

Materials and methods. Twenty-two children with sickle cell disease and no history of stroke were evaluated by both TCD and TCDI. Examinations were performed on the same day without knowledge of the other modality results and read independently using manually obtained measurements. Mean velocities, peak systolic velocities, and end diastolic velocities obtained by the two techniques were compared. In a subgroup, manual measurements were compared to electronically obtained measurements.

Results. TCDI values were lower than TCD measurements for all vessels. TCDI TAMMV values were most similar to the TCD values in the middle cerebral artery (–9.0%), and distal internal cerebral artery (–10.8%), with greater variability in the anterior cerebral artery (–19.3%), bifurcation (–16.3%), and basilar arteries (–23.1%). Risk group placement based on middle cerebral artery TAMMV values did not change when comparing the two techniques. Measurements obtained electronically were lower than those obtained manually.

Conclusion. Velocities obtained by TCDI may be lower than TCD measurements, and these differences should be taken into consideration when performing screening for stroke risk and selection for prophylactic transfusion based on the STOP protocol.
Introduction

Cerebral infarction secondary to occlusive vasculopathy occurs in 6–17% of patients with sickle cell anemia by the age of 20 [1–3]. Seventy-five percent of the lesions involve the proximal middle cerebral artery (MCA), distal internal cerebral artery (dICA) and bifurcation (Bif). Stenosis may progress without symptoms for years. Prevention of stroke has been demonstrated with chronic blood transfusion [4] and has been recommended by the National Heart Lung and Blood Institute [5]. Proper selection of patients at high risk for stroke is critical for the application of effective primary prevention. With proper selection, those at risk are detected before stroke develops, while children not at high risk are not unnecessarily exposed to the risks of chronic transfusion therapy.

Transcranial Doppler (TCD) has been shown to predict risk of stroke in children with sickle cell disease [5–9]. Elevated mean flow velocities have correlated with stenosis on angiography [10], increased blood flow, and subsequent stroke [6, 7]. The ability of TCD to identify children at significant risk was the basis for a randomized controlled clinical trial, which showed that the untreated stroke risk of 10% per year could be reduced by blood transfusion to <1% per year. The Stroke Prevention Trial in Sickle Cell Anemia (STOP) identified 130 children with sickle cell disease at high stroke risk on the basis of a time-averaged maximum mean velocity (hereafter referred to as TAMMV) of the MCA, Bif, or dICA of ≥200 cm/s [4]. Velocities were obtained using a 2-MHz nonimaging pulsed Doppler probe (TCD) and manual measurements of all parameters (peak systolic velocity, PSV; end diastolic velocity, EDV; mean flow velocity) by two skilled interpreters. Sixty-three children received periodic blood transfusions, while 67 children received standard supportive care. After 2 years, a stroke had occurred in 10 children in the standard care group, and in only one child in the transfusion group, leading to early termination of the trial. The National Heart Lung and Blood Institute issued a clinical alert recommending TCD screening for cerebrovascular disease every 6 months on all children with sickle cell anemia between the ages of 2 and 16 and consideration of transfusion in those with two abnormal TCD test results [5].

The nonimaging TCD technique used in the STOP study has several advantages. The major advantage is that over 5000 TCD studies have been acquired in a prospective fashion and correlated with outcome. The equipment is low cost in comparison to duplex systems, portable, and can record mean velocities in excess of 300 cm/s. The light-weight transducer with a small foot print has a significant advantage when a small temporal “window” is present. Vessel identification is based on waveform pattern, depth, insonation angle of the Doppler sample volume, and flow direction. This requires considerable operator experience for optimization of velocity recording. All vessels need to be meticulously examined by stepping the sample volume throughout the entire vessel, capturing spectral waveforms at 2-mm increments. Limitations of the nonimaging transcranial Doppler (TCD) include inability to visualize intracranial anatomy, making positive vessel identification difficult/inaccurate in some patients. There may be a long learning curve for inexperienced examiners. The required examination and interpretation protocols, including manually measuring velocities, are labor intensive and could be inaccurate in poorly trained hands. In addition, these machines are not readily available in radiology departments, often requiring special purchasing for the sole use of TCD studies, which may not be practical in centers with small sickle cell patient populations.

Transcranial Doppler imaging (TCDI) is available on most ultrasound machines with 2- to 3-MHz transducers and color Doppler capability. Advantages of this technique include a shorter learning curve, as sonographers are already trained to use the equipment. The intracranial vessels are visualized, providing increased confidence in vessel identification and sample volume placement for spectral waveform acquisition. The color image documents vascular anatomy, flow direction, branch patterns, and tortuosity. Other pathology, such as arteriovenous malformations, aneurysms, and hematomas may be identified. Angle correction is available, though currently it has not been applied to TCD protocols. Measurements can be electronically calculated, shortening the time spent obtaining the data.

Disadvantages of TCDI include larger, heavier transducers. The moderate increase in size of the footprint may create insonation difficulties in patients with small temporal “windows.” Examiners may concentrate on the image rather than the audio characteristics, an integral component of waveform optimization and documentation of the highest mean flow velocity. Studies have noted differences in TCDI velocities as compared to TCD velocities when performed on the same patient [11, 12]. These variations may be the result of differences in instrumentation, angle of insonation, and measuring technique, which may impact velocity readings. With the STOP protocol recommending therapy when two separate studies identify velocities at or over 200 cm/s, it is important to document whether different techniques do in fact result in similar velocity measurements prior to therapy initiation. Accurate correlation of TCD and TCDI velocities would be desirable, allowing TCDI operators who follow the STOP examination protocol to relate their findings to the large body of published prospective TCD prediction information.

The purpose of this study was to compare transcranial Doppler velocities obtained with TCDI using manual or electronic measuring techniques to those acquired