

Transcranial Doppler screening for stroke risk in children with sickle cell disease: a systematic review.

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Abstract

Background: Sickle Cell Disease (SCD) is one of the most common causes of stroke in children worldwide. Based on the results of the Stroke Prevention Trial in Sickle Cell Anaemia (STOP), annual Transcranial Doppler Ultrasound (TCD) screening for affected children is standard practice. However, the need for TCD surveillance programmes could override the accuracy of the screening, affecting the correct stratification of stroke risk and subsequent clinical management of the target population.

Aims: To shed light on this issue, a systematic review of the literature on TCD screening for children and adolescents with SCD was carried out (CRD42016050549), according to a list of clinically relevant questions, with a particular focus on screening practices in European countries. Quality of the evidence was rated using GRADE.

Summary of review: Thirty-three studies published in English or French were included (5 randomised controlled trials, 8 experimental non-randomised and 20 observational studies). The quality of the retrieved evidence ranged between low and high, but was rated as moderate or high most of the times. TCD is effective as a screening tool for primary prevention of stroke in SCD children. There is no high quality evidence on the effectiveness of alternative screening methods, such as imaging-TCD (TCDi) with or without angle correction or magnetic resonance angiography (MRA). No evidence was found on effectiveness of the screening on children on hydroxyurea and with genotypes other than HbSS and HbS/β0. No European data were found on screening rates or adherence of screening practices to the STOP protocol.

Conclusions: High quality studies on alternative screening methods that are currently used in real-world practice, and on screening applicability to specific subgroups of patients are urgently needed. Considering the low awareness of the disease in European countries and the lack of data on screening practices and adherence, clinicians need up-to-date guidelines for more uniform and evidence-based surveillance of children with SCD.

Introduction

In Europe, Sickle Cell Disease (SCD) has been traditionally regarded as a “rare” disease;¹ however, at present it is the most common severe genetic disease in the United Kingdom and France, with 10 000-15 000 patients in each country.² Worldwide, SCD, in its homozygous form, HbSS (also called “Sickle Cell Anaemia”, SCA), is one of the leading causes of stroke in children, with a heavy burden of subsequent disability and cognitive impairment.³⁻⁵ In the absence of prevention programmes, stroke accounts for up to 10% of deaths in SCD,⁶ which overall results in a reduction of 25 to 30 years of life expectancy.^{7,8} Children with SCD have a 410-fold increase in ischaemic stroke risk as compared to their peers;^{3,9} 11% of patients with SCA have a stroke by the age of 20, with highest incidence during the first decade and a high proportion of recurrent strokes.¹⁰ In 2014, the National Heart, Lung, and Blood Institute (NHLBI) published the American guidelines for SCD. This was prompted by the lack of continuity in management of SCD, and by the need to inform health care professionals.¹¹ The NHLBI guidelines recommended annual transcranial Doppler (TCD) screening for primary prevention of stroke in children with HbSS and HbS/β0 between 2 and 16 years. For these children, TCD surveillance is considered standard management, as a result of the Stroke Prevention Trial in Sickle Cell Anaemia (STOP),¹² and chronic transfusion programmes have been implemented in many countries.^{11,13} However, in the US screening remains inadequate,¹⁴ and there is significant heterogeneity among centres in its delivery; moreover, many ongoing practices are not supported by evidence.¹⁵ While strict adherence to the STOP protocol (Table 1) is critical for correct stratification of stroke risk and subsequent clinical management, the need for TCD surveillance programmes could override the accuracy of the screening.^{16,17}

The aim of this paper is to carry out a systematic review of the available evidence to answer the following clinical questions: is TCD effective as a screening tool for SCD children at high risk of stroke? Is TCD-imaging (TCDi) with or without angle correction a suitable alternative to

conventional TCD? What is the best TCD screening protocol? Whom does TCD screening apply to? Is additional/alternative screening ever needed? What is the rate of TCD surveillance programme delivery in European countries?

Methods

A panel composed of health care professionals with expertise in the areas of neurosonology, cerebrovascular diseases, paediatric haematology and vascular ultrasound, agreed on a list of clinically relevant questions to inform the literature search (Table 2). We included randomised controlled trials, non-randomised experimental studies and observational studies about TCD screening for children and adolescents (aged less than 18 years) with SCD. Case reports and small case series were not included. The protocol of this systematic review was registered in PROSPERO (CRD42016050549).¹⁸

Search strategy and selection criteria

One member of the review team (SM) carried out the literature search and then two researchers (SM, TSP) independently selected the relevant references and critically appraised the included studies. A modified version of the PICO table was used to inform the search strategy (Appendix A, online material). Any discrepancies about the inclusion or exclusion of references were resolved by consensus and arbitration by a third member of the review team (MD). The panel identified all relevant studies published up to April 30th 2016 on TCD screening for risk of stroke in children with SCD, by searching the following databases: MEDLINE, the Cochrane Central Register of Controlled Trials, Web of Science, Embase, CINAHL, Scopus and LiLACS. As a check for unpublished trials, an additional, specific search was carried out using *clinicaltrials.gov*, the international clinical trials' registry. The following search strategy was used:

- *Explicit search strategy:* title/abstract = (anemia* or Sickle Cell* or Hemoglobin S Disease* or Sickle Cell Disorder or HbS Disease*) AND (child* or boy* or girl* or juvenil* or minors or paediatric* or pediatric* or pubescen* or school* or student* or teen* or young or youth*) AND (screening tool* or protocol* or training standard*);
- *MeSH search strategy:* "Ultrasonography, Doppler, Transcranial"[Mesh]" AND "Anemia, Sickle Cell"[Mesh]; ("Ultrasonography, Doppler, Transcranial"[Mesh]) AND ("Anemia, Sickle Cell"[Mesh]) AND "Adolescent"[Mesh]; "Ultrasonography, Doppler, Transcranial"[Mesh] AND "Anemia, Sickle Cell"[Mesh] AND "Child"[Mesh]; "Ultrasonography, Doppler, Transcranial"[Mesh] AND "Child"[Mesh] AND "screening".

Existing evidence-based clinical practice guidelines were screened and relevant studies incorporated, where appropriate. Reference list of included studies and systematic reviews about SCD were also checked for additional studies. Findings from the present systematic review were reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.¹⁹

Evidence quality rating

The quality of the randomised studies was rated using the Cochrane Risk of Bias tool (http://handbook.cochrane.org/chapter_8/8_assessing_risk_of_bias_in_included_studies.htm).

The Grading of Recommendations Assessment, Development, and Evaluation (GRADE) system²⁰ was then used to assess the quality of the overall evidence for each specific clinical question. Although the quality of evidence represents a continuum, the GRADE approach results in four grades (<https://gradepro.org/>): *high* (researchers are very confident that the true effect lies close to that of the estimate of the effect), *moderate* (the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different), *low* (the true

effect may be substantially different from the estimate of the effect) or *very low* (the true effect is likely to be substantially different from the estimate of effect).

Results

Overall, 187 citations were identified by the MeSH terms search and 18 additional references were obtained with the explicit search method. Fifty-six potentially eligible articles were retrieved in full text (54 in English, 1 in French and 1 in Italian). We excluded 14 reports, resulting in 42 publications corresponding to 33 primary studies (5 RCTs, 8 experimental studies and 20 observational studies), published between 1988 and 2016 (Figure 1 and Appendix B, online material). Almost all the included studies were published in English and only one in French. According to GRADE, the quality of the retrieved evidence ranged between low and high, but was rated as moderate or high most of the times. For graphical representations of our judgements of risk of bias for the RCTs and for the summary of findings table, see Appendix C and D of the online material, respectively. Following the review protocol, we structured the presentation of the results according to the above-mentioned specific clinical questions.

Is TCD effective as a screening tool for SCD children at high risk of stroke?

The STOP trial showed the efficacy of TCD screening for prevention of stroke in HbSS and HbS/β0 children between the age of 2 and 16 without history of stroke.^{12,21} Among these children, a TCD time-averaged mean of the maximum velocity (TAMMV) ≥ 200 cm/sec in the Middle Cerebral Artery (MCA) and/or terminal Internal Carotid Artery (tICA) effectively identifies those at highest risk of ischaemic stroke.^{12,22} As a result, TCD surveillance is now considered standard management for the prevention of first-ever stroke in children with HbSS and HbS/β0 between the age of 2 and 16.^{11,13,23,24}

What is the best TCD screening protocol?

The only TCD screening protocol with demonstrated efficacy for the selection of patients for transfusion is the STOP protocol (Table 1).^{12,25} The STOP protocol was designed to obtain the highest TAMMV through meticulous examination of small increments in depth through the MCA/tICA, trying to identify the highest velocities.²⁶ When a TCD recording has adequate signal-to-noise ratio, the waveform follower will tightly track the highest velocities and will accurately calculate the TAMMV. In cases of poor signal-to-noise, the TAMMV can be read manually, according to the STOP reading protocol.^{26,27} The cut-off point selected to define “high risk patients” (about 45% risk over 4 years) was MCA/tICA velocity ≥ 200 cm/sec (Figure 2), while if all velocities were less than 170 cm/sec, the results were considered to be normal. MCA/tICA velocities in the range between 170 and 199 cm/sec were considered as “conditional”, and implied tighter controls for the child.¹² Following this protocol, a sample of children screened for the first time would be expected to have a distribution of 70% normal, 15% conditional, 10% abnormal, and 5% inadequate TCD scans.¹² Further analysis of the STOP trial suggested that in the absence of high-risk ICA/MCA velocities, high (≥ 170 cm/sec) Anterior Cerebral Artery (ACA) velocities are associated to increased risk of stroke.²⁸ Also, among children with ICA/MCA velocities in the high risk range, having ACA velocities ≥ 170 cm/sec confers more than twice the risk of stroke as compared to having normal ACA velocity.

Is TCD-imaging, with or without angle correction, a suitable alternative to conventional TCD?

Transcranial Color-coded Duplex techniques, also called TCD-imaging (TCDi), were not investigated in the STOP study. Although there is no theoretical reason for a discrepancy between velocity measured with TCD and TCDi, there is conflicting evidence on this point in the literature, with some studies finding that TCDi velocities are lower than those obtained with

TCD.^{17,29-31} On this basis, an adjustment by 10-15% of TCD STOP velocity thresholds has been suggested for TCDi velocities classification.^{13,16}

TCDi techniques allow Doppler angle correction; angle-corrected TCDi velocities are higher than uncorrected values³¹. In one study that found uncorrected TCDi velocities to be consistently lower than conventional TCD, TCD and angle-corrected TCDi velocities were not statistically different in MCA and tICA.³¹ This is conflicting with other studies where TCDi without angle correction and TCD yielded comparable velocities in the MCA and tICA.^{16,32} Because the STOP velocity thresholds were based on conventional TCD, which doesn't allow angle correction, angle-corrected TCDi scans might result in calculated velocities that are higher than those that would have been obtained using conventional TCD.²⁶ Of notice, different TCDi machines can use different terms for TAMMV, according to the manufacturer.²⁶ Given the conflicting evidence from moderate quality experimental and observational studies, further high quality studies validating appropriate thresholds for TCDi with and without angle correction are desirable.²⁷

Whom does TCD screening apply to?

Results from the STOP trial apply to clinically stable patients with HbSS and HbS/β0 genotype aged 2 to 16 without history of stroke, free from medications which might confound the interpretation of the results.^{12,25} Hydroxyurea is now standard therapy in SCD patients with a history of acute chest syndrome and/or recurrent, severe pain episodes,¹⁵ and it is also known to decrease TCD velocities.³³⁻³⁵ Whether TCD screening of children on Hydroxyurea provides any clinical benefit is uncertain.

There is also limited information on the clinical benefit of screening patients with sickle-related genotypes other than HbSS and HbS/β0, such as HbSC or HbS/β⁺. HbSC patients have a high incidence of stroke, although at a later stage in life as compared to HbSS children.⁵ A recent

observational study including 144 HbSC and 27 HbS/β⁺ out of 572 total participants from a Mali population, reported a low frequency (1.5%) of HbSC patients having conditional velocities, and no patients with abnormal TCD reading, as compared to 17.3% conditional HbSS and 8.1% high risk, suggesting that the TCD profile is different in the two genotypes.³⁶ Whether screening HbSC patients in childhood is clinically useful is uncertain.¹⁵

Is alternative/additional imaging ever needed?

Magnetic Resonance Angiography (MRA) is the most studied and used alternative screening method, being reliable and safe in terms of radioprotection.^{37,38} However, the STOP trial did not provide data on stroke risk detected by MRA alone, so that MRA cannot replace TCD as an alternative imaging tool in primary prevention.^{39,40} In cases of inadequate TCD scans (5% of screened patients) an estimate of risk cannot be obtained by TCD because of technical reasons, although among children screened for the STOP trial, those with inadequate scans had a risk of stroke similar to those with normal scans.^{39,41} On the other hand, very low TCD velocities (≤ 70 cm/sec) may indicate severe arterial stenosis associated with high risk of stroke.⁴² In both these cases, MRA could help distinguish technical problems from advanced occlusive disease.³⁹ In the STOP trial, TCD velocities were likely to remain abnormal over time even under optimal treatment in patients with abnormal MRA findings, as opposed to TCD velocities in transfused patients with normal MRA, which tended to revert to normal. This suggests that MRA in children with high velocities can help clinical management and interpretation of follow-up TCD scans.³⁹

What is the rate of TCD surveillance programme delivery in European countries?

There are no European data on TCD screening rates among SCD children. In the US, there are observational studies reporting on screening rates, predictors of TCD screening compliance, and

adherence of screening protocols to the original STOP protocol.^{14,15,43-48} Data are usually drawn from Medicaid programs for states with an average-to-high prevalence of SCD: Florida, Illinois, Louisiana, Michigan, South Carolina, Texas, Tennessee. Overall, although rates of TCD screening have been increasing through the years, they remain unsatisfactory, with the most recent figures (2010) being around 44%.⁴⁵ Many factors influence the rate of screening among affected children, like maternal education and frequency of contacts with health care providers.¹⁵ As to adherence of screening practices to the original STOP protocol, there is wide heterogeneity among centres in the US, with many clinical practices not supported by evidence, such as screening of sickle-related genotypes other than HbSS, and using MRI as a screening tool. Small institutions with low number of children are more likely to follow practices not fully evidence-based.¹⁵ Given the increasing burden of SCD in Europe, data on screening rates and practices in European countries are highly desirable to inform surveillance programmes.

Discussion

This systematic review on TCD screening for risk of stroke in children with SCD revealed paucity of high quality studies on many relevant clinical questions, and either contradicting, moderate-low quality evidence, or lack of evidence on others. We decided to use the GRADE methodology because it is a transparent and replicable way to assess both randomised and observational studies. Even though we could not adopt the detailed methodology recommended for its full implementation, we followed the spirit of the GRADE approach to carefully assess the quality of all available information, which was relevant to each clinical question. Most of the high quality evidence retrieved is based on the STOP trial.

The STOP TCD protocol has some relevant differences as compared to routine clinical TCD scanning practice, and there is lack of evidence that alternative protocols would be equivalent in selection of candidates for transfusion.²⁶ Diversion from the STOP protocol could result, on one

hand, in underestimation of high-risk TCD velocities and increased risk of stroke; on the other, in overestimation of velocities with unnecessary blood transfusions. The need for TCD screening, prompted by the STOP results, could outweigh concerns regarding the accuracy of TCD screening, particularly in low-income countries or where there are small numbers to screen. Even where the TCD surveillance programme is applied, there are many factors that might affect its success including the lack of adequately trained TCD operators and lack of standardisation with respect to the STOP protocol.¹⁵⁻¹⁷ TCD operators should achieve competency through recognised TCD training programmes and with regular audit of TCD scan numbers.^{13,49}

TCDi techniques were not explored in the STOP trial, but potentially have some advantages as compared to TCD, such as more expedite identification of intracranial vessels, and the availability of Doppler angle correction, which has the potential to improve the accuracy of blood flow velocity measurement.³⁰ Its use has facilitated implementation of surveillance programmes, particularly in areas of limited access to TCD equipment or expertise.²⁹ However, there is conflicting evidence on the comparability of results obtained with TCDi with and without angle correction as compared to conventional TCD.^{16,17,29-32}

Our systematic review revealed that evidence is lacking in many other clinically relevant areas. Research is needed to address the gaps in our knowledge in applicability of the screening to children with genotypes other than HbSS and HbS/β0, or on chronic treatment with hydroxyurea. This is particularly relevant after the recent publication of the results of the TWiTCH trial,³⁵ which still need to be confirmed in real-world practice.

In Europe, SCD has been regarded as a rare disease, relegated to the Mediterranean regions of the South of Europe. Orphanet, the reference portal of a consortium of around 40 European countries for information on rare diseases and orphan drugs, lists SCD among the rare diseases.¹ We could find no European data on screening rates or adherence of screening practices to the STOP protocol. In the US screening remains unsatisfactory; we expect that screening rates and

adherence to the STOP protocol in Europe could be even lower. As part of the process for identifying clinically relevant issues and potential areas of uncertainty around the topic “screening for risk of stroke in children with SCD” for the literature search, a survey was held among neurosonologists attending the 19th Meeting of the European Society of Neurosonology and Cerebral Hemodynamics (ESNCH) in 2014, looking at differences in TCD screening practices among practitioners from different parts of Europe.⁵⁰ The survey showed wide heterogeneity on technical aspects of the TCD screening, including the choice of the screening tool (TCD, TCDi, MRA), reference velocity thresholds, SCD genotypes screened, concomitant treatments and acceptable training standards (Appendix E, online material). This observation reinforces the concept that in Europe, there is still limited awareness on SCD and standards in SCD are not being adhered to, even among a selection of experts in the clinical application of ultrasound. Clinicians and health providers need to be aware of the serious complications related to SCD and the global impact of the disease.^{8,11}

As all systematic reviews, this paper has some limitations. We did our best to identify all the potentially eligible studies from our searches of published and unpublished data, however we cannot rule out the possibility that some relevant papers are missing. In order to reduce the risk of excluding important information, this study was carried out by a multi-disciplinary review team and experts in the field were contacted, if necessary. However we didn’t address clinically relevant issues such as screening for risk of stroke in the adult population. Stroke is a problem in adults as well as children, with an incidence of 0.5%/year in 20 to 29 year olds, 0.6%/year in 30 to 39 year olds, and 0.7%/year in 40 to 49 year olds, 10 times greater than in Africans Americans without SCD.^{5,51} Nevertheless, there is a lack of prospective data on the risk of stroke in SCD adults in relation to TCD velocities. A comparison of TCD results in adult SCD patients with a history of stroke or TIA with asymptomatic patients found no significant difference in TCD velocities. Cut-off used for paediatric population cannot be applied to the adult population, as

intracranial velocities gradually decrease after 6 years of age.⁵²⁻⁵⁴ A velocity of 123.5 cm/s or higher in the tICA or MCA accurately detected intracranial stenosis in a study on adults with SCD,⁵⁵ but has neither been validated in an independent population nor been demonstrated to predict risk of stroke.⁵¹ There is no evidence that TCD can be applied to asymptomatic SCD adults as a screening tool for stroke risk, although detection of intracranial arterial stenosis could help clinical management of these patients.⁵⁴

In conclusion, this systematic review revealed a lack of high quality evidence in many clinically relevant areas of TCD screening for risk of stroke in children with SCD. In Europe, this is a neglected issue that needs more awareness among clinicians. There are no data on screening practices or on adherence to the STOP TCD screening protocol in Europe; operators need up-to-date guidelines for accurate delivery and interpretation of surveillance.

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Figure and table Legends

Figure 1: PRISMA flow chart of included and excluded studies, with reasons.

Figure 2: Example of MCA TCD tracing in the “high risk range” obtained from a 7-year-old female HbSS patient.

Table 1. TCD/TCDi protocol for the screening of children with SCD. TCD=Trancranial Doppler;

TCDi= Transcranial Doppler-imaging; SCD=Sickle Cell Disease; MRA= Magnetic Resonance

Angiography; MCA= Middle Cerebral Artery; ICA=Internal Carotid Artery; ACA= Anterior Cerebral

Artery; PCA= Posterior Cerebral Artery; TAMMV= time-averaged maximum velocity.

Table 2. Potential sources of inconsistency in the screening for stroke risk in children with SCD

TCD=Trancranial Doppler; TCDi= Transcranial Doppler-imaging; SCD=Sickle Cell Disease;

MRA=Magnetic Resonance Angiography; TAMMV= time-averaged maximum velocity.

TCD/TCDi PROTOCOL

- Patient supine, calm and awake; no fever, no infections.
- Doppler sample volume 4-7mm, set spectral gain level so noise is just visible
- Use the following criteria for vessel identification:
 - Transducer position
 - Transducer angulation
 - Sample volume depth
 - Flow direction
 - Relative position of Doppler signals
 - Parenchymal and bony landmarks (for TCDi)
 - Spatial position of blood vessels (for TCDi)
- Advance the sample volume depth at 2mm intervals throughout each vessel examined
- **The transducer/vessel orientation must be optimised at each depth increment to obtain the highest possible audible Doppler frequency which equates to the highest velocity**
 - Always record the highest mean of the TAMMV
- Record velocities from:
 - Distal MCA and then at 2mm along the MCA up to the bifurcation
 - MCA/ACA bifurcation
 - ACA
 - Terminal ICA
 - PCA
 - Basilar artery
- TAMMV Thresholds in MCA/TICA/ACA
 - Inadequate scan, or velocity <70 cm/sec, or asymmetry in velocity >50% of contralateral MCA
 - Normal: 170 cm/sec
 - Conditional: 170-199 cm/sec
 - Abnormal: ≥ 200 cm/sec
- TCD surveillance intervals:
 - Inadequate-repeat scan (if patients uncooperative)
 - Normal - annual surveillance
 - Conditional - 3 monthly surveillance
 - Abnormal - repeat within 2 weeks if <220cm/s or consider transfusion immediately if TAMMV ≥ 220 cm/s

Table 1. TCD/TCDi protocol for the screening of children with SCD.

- ✓ Choice of the screening tool (TCD as opposed to alternative tools such as TCDi and MRA)
- ✓ TCD cutoff for risk classification (based on TAMMV as opposed to other TCD parameter used in clinical practice to estimate entity of arterial stenosis)
- ✓ Appropriate threshold for stroke risk classification in the TCDi protocol
- ✓ Use of angle correction in the TCDi protocol
- ✓ Applicability of TCD screening to specific subgroups of SCD patients (children on hydroxyurea; with genotypes other than HbSS and HbS/β0; adult patients)
- ✓ Role of MRA in the screening protocol

Table 2. Potential sources of inconsistency in the screening for stroke risk in children with SCD.