National Haemoglobinopathy Panel

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BACKGROUND

Sickle cell disease (SCD) is one of the most common inherited disorders in the world. Stroke affects 5-11% of patients under the age of 20 with HbSS, the highest incidence occurs between the ages of 1-9 years with recurrence in over half the children within 1-2 years of the original stroke[1, 2]. The disease process is an occlusive vasculopathy favouring the terminal, intracranial internal carotid artery (TICA) and the proximal parts of the middle cerebral artery (MCA) and anterior cerebral artery (ACA) but spares the posterior cerebral and basilar arteries. The randomised controlled Stroke Prevention Trial in Sickle Cell Anaemia (STOP 1) compared exchange transfusion to medical therapy in children with SCD and demonstrated a 92% reduction in stroke risk in the transfusion arm of the trial[3]. The patients were selected based on Transcranial Doppler Ultrasound (TCD) measurement of a maximum time-averaged maximum mean velocity (TAMMV) of ≥200cm/s in either the MCA or TICA. This trial established definitive TCD criteria for identifying children in crisis who would benefit from blood exchange transfusion.

PURPOSE

The protocols for TCD scanning and stroke risk categorisation are based on the criteria developed from the first STOP trial which used non-imaging TCD. However, both non-imaging TCD and imaging TCD (TCDi) are effective methods to examine children with SCD, provided that correct technique and optimisation are used to measure the TAMMV. TCD measurements are used to establish stroke risk and identify children for referral for exchange transfusion therapy and contribute to planning of the next surveillance scan interval to monitor stroke risk.

COMMON INDICATIONS

TCD screening is indicated for all children between the ages of 2-16 years with a diagnosis of homozygous sickle cell anaemia (HbSS), β-thalassemia (HbS β zero-thal) and in some centres also for Sickle-C disease (HbSC). Ongoing TCD scanning is recommended once a child has started transfusion[4].

CONTRAINDICATIONS AND LIMITATIONS

- A small percentage of children will have limited scans due to attenuation of ultrasound – these can be identified on imaging-TCD by poor or absent visualisation of parenchymal or bony landmarks, (approximately 5-7% incidence) - use alternative imaging modality
- Changes in velocity may not always be due to SCD - Velocity will be **decreased**:

- Following transfusion which decreases velocity for several days post transfusion - perform TCD assessment at least 2 weeks after transfusion[5].
- Hyperventilation decreases pCO_2 levels and reduces velocity - wait until the child is calm

o Changes in velocity may not always be due to SCD - velocity will be **increased** with:

- Fever
- Sleep
- Crying
- Sickle chest syndrome
- Hypoxia
- Worsening anaemia
- Significant hypoglycaemia

Results obtained under these conditions will be unreliable. It is advisable to avoid scanning when they are present however, any result obtained can be reviewed by the clinician and the decision for a repeat scan made at this time.

○ Errors due to operator experience

- Non-imaging TCD requires established operator experience. The Doppler angle is unknown – the operator must optimise transducer/vessel orientation to achieve the smallest Doppler angle and thus the highest Doppler frequency and maximum detectable velocity.
- Imaging TCD errors can be introduced due to operator emphasis on the colour image resulting in underestimation of TAMMV. Erroneous use of Doppler angle correction will result in overestimation of the TAMMV.

PATIENT COMMUNICATION

- Obtain and record a clinical history which should include information on:
  - Presence of fever
  - Review of previous TCD history
  - Timing of last transfusion
  - Relevant medications or therapies (optional)
- Ensure that the patient remains calm but awake throughout the examination

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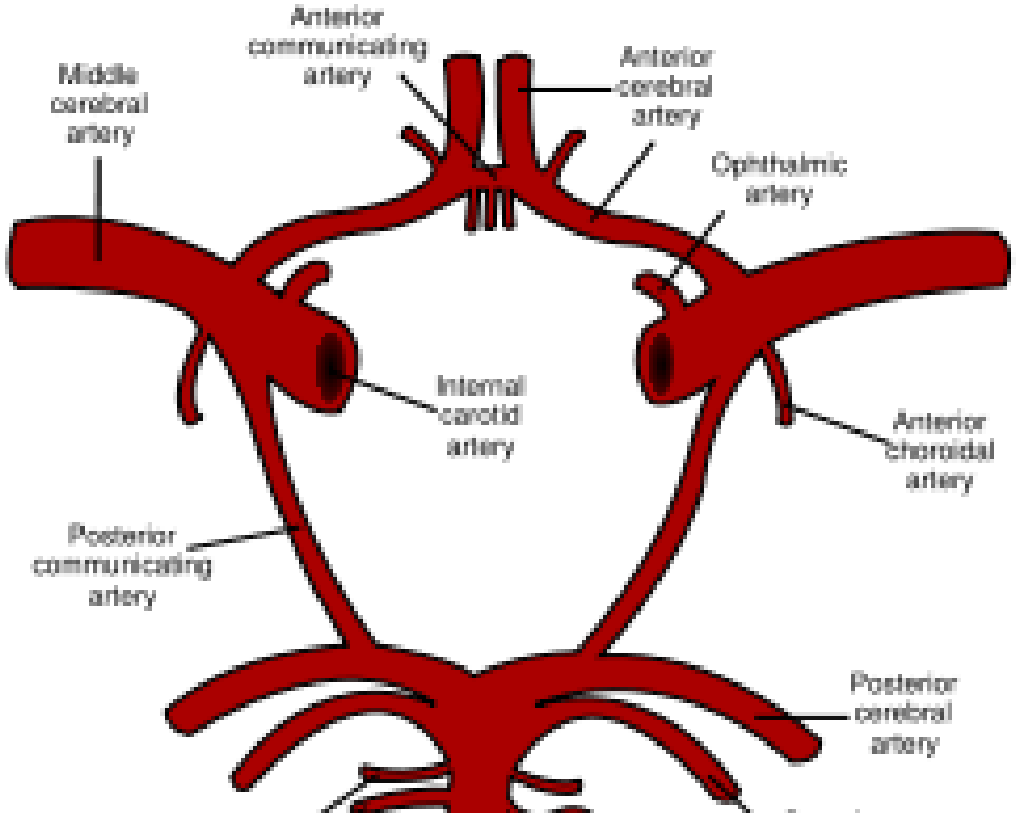

NON-IMAGING TCD

- **Equipment & settings:** 2MHz pulsed Doppler velocimeter with spectral display and automated velocity measurement using a maximum frequency follower, which should track the maximum frequency faithfully in order to measure the true TAMMV velocity. Doppler sample volume size 5mm. Set power to minimum possible to obtain signals transcranially.
- MCA/ACA Bifurcation - Position the transducer just above the zygomatic arch. Starting at the temporal bone set the sample volume depth to 4cms, then using 1 or 2mm changes, increase the sample volume depth until a bi-directional signal is obtained, this is the bifurcation where the intracranial internal carotid artery (TICA) terminates and flow from the MCA (antegrade flow) and ACA (retrograde flow) are observed.
- Middle cerebral artery – From the bifurcation decrease the sample volume depth in 1-2mm intervals. **At each decrement – optimise the transducer/vessel angulation so that the highest audible Doppler frequency, and therefore highest detectable TAMMV, is obtained and recorded from the MCA.**
- Terminal internal carotid artery– Return to the bifurcation, angle the transducer inferiorly to detect velocities from the TICA towards the transducer, optimise angle and record maximum TAMMV.
- Anterior cerebral artery – Return to the bifurcation, angle the transducer superiorly and optimise the transducer angle and obtain velocities from the ACA (retrograde flow), acquiring velocities at 1-2mm intervals, record the maximum TAMMV.
- Posterior cerebral artery - Return the sample volume to the ICA bifurcation depth, and angle the transducer posterio-inferiorly to obtain signals from the posterior cerebral arteries (PCA), this is usually at 5.0-6.0cm in children. Record velocities at 1-2mm intervals until the mid-line is reached, where the bi-directional signal from the right and left PCA can be visualised, record the maximum TAMMV from the PCA.
- Record at least two velocities from the MCA and TICA and at least one velocity from the ACA and PCA.
- If the signal-to-noise ratio is poor, the maximum frequency follower may become inaccurate, in these cases a manual measurement can be performed by measuring the peak systolic (PSV) and end diastolic velocities (EDV) where:

$$\mathrm{TAMMV} = (\mathrm{PSV} + (2.\,\mathrm{EDV}))/3$$

IMAGING TCD PROTOCOL

- **Equipment & settings:** Ultrasound colour flow mapper with TCD imaging transducer. Use a phased array transducer with a small imaging foot print, an imaging frequency range of 1-5MHz and colour flow and Doppler frequency of 1.6 to 2MHz. Set the Doppler sample volume size to 4-6mm (dependent on the system). Set power to minimum possible to obtain signals transcranially. Measure the time-averaged maximum velocity (TAMMV) using the automated velocity measurement (maximum frequency follower). Acquire at least two velocities from the MCA, TICA and ACA and one velocity from the PCA and store velocities to PACS.
- **Imaging landmarks on B mode**
  - Bony: Bright echogenic signal from the lesser sphenoid wing
  - Parenchymal: Echolucent signal from the butterfly-shaped brainstem
  - A clear image of both structures will indicate the quality of the acoustic window
- **Velocity optimisation and duplex scanning**

  A critical part of the imaging protocol is the method of transducer orientation and optimisation to measure the highest achievable maximum TAMMV (there are several synonymous acronyms including TAMX and TAPV, please check for your system). The colour flow image provides an anatomical map of the position of the basal cerebral arteries. **Doppler angle correction is not used for velocity measurement.** Once the vessel is located the operator must perform fine transducer/vessel adjustments while listening to the audio Doppler signal and track through the vessel, taking note of colour flow evidence of aliasing or turbulence, until the highest Doppler frequency is obtained and the maximum obtainable TAMMV recorded.
- MCA/ACA bifurcation - Identify the bifurcation on the colour flow image, at the point where colour flow changes from red to blue and a bi-directional flow-velocity signal can be obtained on pulsed Doppler
- Middle cerebral artery - Projects near the medial aspect of sphenoid wing and anterior to the brainstem. From the bifurcation signal, reduce the sample volume depth and track the MCA (forward flow) to the periphery, measure serial velocity recordings at 2mm intervals. Colour flow should be coded red indicating flow towards the transducer. Repeat transducer/vessel optimisation at each step.
- Anterior cerebral artery - From the bifurcation signal, increase sample volume depth for flow along the ACA – flow colour-coded blue, away from the transducer (in normal conditions)

- Posterior cerebral artery - The PCA is visualised as it courses around the brainstem. P1 segment colour flow red, towards transducer, P2 segment colour flow blue, away from transducer as it encircles cerebral peduncle
- Terminal internal carotid artery - Visualise the MCA/ACA bifurcation (bi-directional flow), angle transducer inferiorly and increase sample volume depth by 5mm, colour-coded flow will be red, towards transducer, although in the supraclinoid segment blue colour-coded flow (reverse) may be seen.
- If the signal-to-noise ratio is poor and the maximum frequency follower is inaccurate, a manual measurement can be performed using the peak systolic (PSV) and end diastolic velocities (EDV) where:

$$\mathrm{TAMMV} = (\mathrm{PSV} + (2.\mathrm{EDV}))/3$$

OPTIONAL MEASUREMENTS

Basilar artery

- Ask the patient to lie on their side and obtain signals from the vertebral and then basilar arteries, usually obtained at between 7.0-8.0cms.
- For measurements via the *occipital* approach, the transducer is positioned in the mid-line of the foramen magnum and directed parallel to the sagittal plane. Velocities are obtained from the intracranial part of the vertebral arteries and from the basilar artery. The distal vertebral arteries can be tracked cephalad until they form the basilar artery at a depth of between 10 to 12.5cms.

Extracranial Internal carotid artery

- Examination of the cervical ICA was not part of the STOP trial and related recommendations. There is, however, increasing evidence that extracranial internal carotid artery (eICA) stenosis in children with sickle cell disease is an independent risk factor for silent cerebral infarction[6, 7]. Two approaches have been described:
  - For non-angle corrected studies, the phased array transducer is directed sub-mandibularly to measure the highest velocities in the eICA. A **TAMMV** of ≥ 160 cm/s is used as the threshold for significant stenosis.
  - For angle-corrected studies using a high resolution, linear array transducer, conventional duplex scanning of the eICA is performed. A peak systolic velocity **(PSV)** of ≥ 300 cm/s is indicative of stenosis which can be located at any level in the eICA.
  - The highest TAMMV or PSV velocity and imaging approach should be included in any report.

DIAGNOSTIC CLASSIFICATION

Stroke risk is currently based on the time-averaged maximum mean velocity from the; MCA, TICA & ACA. Although a bilateral scan is performed, the single highest TAMMV determines the STOP classification.

- NORMAL – All TAMMV less than 170 cm/sec
- CONDITIONAL – A TAMMV of at least 170 cm/sec but less than 200 cm/sec in one or more of the three designated vessels
- ABNORMAL – TAMMV of at least 200 cm/sec in any one of the MCA, ACA or TICA.
- LOW VELOCITIES – TAMMV <70cm/s or ASYMMETRY of >50% in one or more of the three designated vessels
- NON-DIAGNOSTIC – Velocity not measurable due to patient compliance or poor imaging window. Repeat scan if poor compliance.
- INADEQUATE – A study that does not provide readings from right and left MCA/ICA/ACA would be classified as inadequate however, if one vessel is clearly abnormal this scan should be classified as INADEQUATE but ABNORMAL.

SURVEILLANCE INTERVALS

The timing of repeat TCD scans will be influenced by prior TCD results, clinical examination and other results, the final decision regarding the repeat scan interval will be made by the clinician. The STOP trial and subsequent studies have recommended the following intervals[4,8].

- NORMAL findings: Re-scan annually up to the age of 16, then discharge to adult programme
- CONDITIONAL findings: Re-scan within 1 month for children under 10 years and children with velocities at upper limit of conditional (185-199cm/s) and re-scan in 3 months for children aged 10 years and over.
- ABNORMAL findings:
    - If initial TAMMV is ≥220cm/s – patient to be reviewed immediately by Clinician (consideration for transfusion or alternative treatment).
    - If initial TAMMV is 200-219cm/s repeat scan within 1-2 weeks.
        - If values remain in abnormal range on second scan – patient will be reviewed by Clinician immediately (consideration for transfusion or alternative treatment)
    - If values drop to the conditional range, repeat scan within 3 months.

- LOW VELOCITIES – Indicative of possible occlusion, perform additional imaging (MRA or CTA) for confirmation of pathology.
- NON-DIAGNOSTIC – Consider alternative imaging for non-diagnostic scans
- TRANSFUSION – Abnormal velocities may revert to normal in patients on transfusion.
    - Keep children on surveillance using the above intervals but if abnormal velocities return or persist – patient to be reviewed clinically.
- HYDROXYUREA – Children with abnormal TCD findings which normalised on transfusion, and who changed from transfusion to Hydroxyurea (TWITCH[9]) - rescan 3 monthly until velocities revert to normal, then scan annually.

REPORTING (template)

Results should be communicated to the referring clinician in a clear and timely manner and immediately if values are abnormal or approaching abnormal, the diagnostic report should include:

- The method of scanning (TCD or TCD imaging)
- The diagnostic velocity thresholds applied
- The TAMMV from the MCA, ACA, TICA and PCA
- The final STOP classification

The Clinician will confirm:

- The next planned or recommended surveillance interval
- Treatment decision, where indicated (transfusion)
- Alternative imaging for non-diagnostic or inadequate scans.

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