Clinical Trial

Lancet Haematol
2023 Apr;10(4):e261-e271. doi: 10.1016/S2352-3026(22)00405-7. Epub 2023 Mar 1.

Hydroxyurea with dose escalation for primary stroke risk reduction in children with sickle cell anaemia in Tanzania (SPHERE): an open-label, phase 2 trial

Emmanuela E Ambrose[1], Teresa S Latham[2], Primrose Songoro[3], Mwesige Charles[4], Adam C Lane[2], Susan E Stuber[5], Abel N Makubi[6], Russell E Ware[7], Luke R Smart[8]
Affiliations expand

- PMID: 36870358
- PMCID: PMC10132280 (available on 2024-04-01)
- DOI: 10.1016/S2352-3026(22)00405-7

Abstract

Background: Transcranial Doppler screening with chronic transfusions reduces stroke risk in children with sickle cell anaemia but is not feasible in low-resource settings. Hydroxyurea is an alternative treatment to decrease stroke risk. We aimed to estimate stroke risk in children with sickle cell anaemia in Tanzania and to determine the efficacy of hydroxyurea to decrease and prevent stroke.

Methods: We did an open-label, phase 2 trial (SPHERE) at Bugando Medical Centre, Mwanza, Tanzania. Children aged 2-16 years with a diagnosis of sickle cell anaemia confirmed by haemoglobin electrophoresis were eligible for enrolment. Participants had transcranial Doppler ultrasound screening by a local examiner. Participants with elevated Doppler velocities, either conditional (170-199 cm/s) or abnormal (≥200 cm/s), received oral hydroxyurea starting at 20 mg/kg once daily and escalated every 8 weeks by 5 mg/kg per day to the maximum tolerated dose. Participants with normal Doppler velocities (<170 cm/s) received usual care from the sickle cell anaemia clinic and were rescreened after 12 months to determine whether they qualified for treatment on trial. The primary endpoint

was change in transcranial Doppler velocity from the baseline visit to after 12 months of hydroxyurea treatment, analysed in all patients who had paired baseline and follow-up measurements collected after 12 months of treatment. Safety was analysed in the per-protocol population (all participants who received study treatment). This study is registered with ClinicalTrials.gov, NCT03948867.

Findings: Between April 24, 2019, and April 9, 2020, 202 children were enrolled and had transcranial Doppler screening. Sickle cell anaemia was confirmed by DNA-based testing in 196 participants (mean age 6·8 years [SD 3·5], 103 [53%] were female, and 93 [47%] were male). At the baseline screening, 47 (24%) of 196 participants had elevated transcranial Doppler velocities (43 [22%] conditional, four [2%] abnormal); 45 initiated hydroxyurea at a mean dose of 20·2 mg/kg per day (SD 1·4) with escalation to a mean dose of 27·4 mg/kg per day (5·1) after 12 months. Treatment response was analysed after 12 months (± 1 month; median 11 months, IQR 11-12) and 24 months (±3 months; median 22 months, 22-22). Transcranial Doppler velocities decreased to a mean of 149 cm/s (SD 27) compared with 182 cm/s (12) at baseline, which was significantly lower than baseline ($p<0·0001$), with an average decline of 35 cm/s (SD 23) after 12 months of treatment in 42 participants with paired results available at baseline and 12 months. No clinical strokes occurred, and 35 (83%) of 42 participants reverted to normal transcranial Doppler velocities. Clinical adverse events were mild, and dose-limiting toxicities were uncommon. The most common grade 3 adverse events were malaria (12 [29%] episodes in 45 patients) and sepsis (13 [32%] episodes). There were three serious adverse events, none of which were treatment-related, and no treatment-related deaths occurred.

Interpretation: Children with sickle cell anaemia in Tanzania have a high baseline stroke risk. Hydroxyurea at the maximum tolerated dose significantly lowers transcranial Doppler velocities and reduces primary stroke risk. Transcranial Doppler screening plus hydroxyurea at the maximum tolerated dose is an effective stroke prevention strategy, supporting wider hydroxyurea access for patients with sickle cell anaemia across sub-Saharan Africa.

Funding: American Society of Hematology, National Institutes of Health, Cincinnati Children's Research Foundation.