Brief Communication

Transcranial Doppler Screening in Sickle Cell Disease: Insights from a Regional Study in Karnataka, India

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Abstract

Sickle cell disease (SCD), a hereditary blood disorder in India, disproportionately affects Adivasi communities burdened by socio-economic and systemic inequities. Stroke, a severe complication of SCD, is underexplored in Indian populations, especially among Adivasi groups. This pilot study evaluated the feasibility of transcranial Doppler (TCD) screening in a peripheral healthcare setting in Karnataka, focusing on Adivasi SCD patients. Among 39 participants (27 HbSS, three HbSβ0, nine HbAS) from a hemoglobinopathy registry, none exhibited elevated time-averaged maximum mean (TAMM) velocities, but 73.3% of SCD patients showed unusually low middle cerebral artery (MCA) velocities (<70 cm/s). Significant differences in basilar artery (BA) flow velocities were noted between SCD and sickle cell trait (SCT) patients (p<0.05), while MCA parameters were comparable. The findings establish baseline TCD velocities and highlight the need for region-specific stroke prevention guidelines tailored to underserved Adivasi populations.

Keywords: Karnataka, sickle cell disease, stroke prevention, transcranial Doppler

Introduction

Sickle cell disease (SCD) is a hereditary blood disorder, with India holding the second highest global disease burden. The condition disproportionately impacts marginalized populations, particularly scheduled tribes, who face compounded challenges due to socioeconomic, cultural, and systemic inequities. These vulnerabilities exacerbate SCD outcomes, leading to severe complications like infections, vaso-occlusive crises (VOCs), acute chest syndrome, and strokes, collectively diminishing quality of life and increasing mortality rates.[1] While data on the risk of stroke in individuals with SCD has been progressively increasing over time, there is still a scarcity of detailed information on risk evaluation and management, especially within the Indian context.

Stroke is among the most devastating complications of SCD, affecting both children and adults. In children, strokes, including ischemic events and silent cerebral infarcts, are prevalent, impacting neurocognitive function and long-term quality of life.[2] While the global documentation of stroke prevalence in persons with SCD (PwSCD) is extensive, comprehensive data from India is still scarce. This is especially true for tribal communities, a smaller yet disproportionately impacted group, where genetic clustering and distinct environmental conditions lead to unique phenotypic expressions and possible differences in stroke risk.[1]

Transcranial Doppler (TCD) ultrasonography is considered the gold standard for non-invasive stroke risk assessment in PwSCD. By detecting elevated time-averaged maximum mean (TAMM) cerebral blood flow velocities (≥200 cm/s), TCD identifies children at increased risk of stroke, enabling timely intervention through urgent blood transfusions that can reduce stroke risk significantly.[2,3] Although international guidelines recommend annual TCD screening, especially for Indian children, its adoption remains limited due to resource constraints, lack of trained personnel, and uncertainties about the applicability of global velocity thresholds to Indian populations.[4] This is especially important since the Indian SCD phenotype differs from that of African or African-American populations in terms of disease severity and clinical manifestations, further underscoring the need for region-specific research.[1]

Existing studies across countries illustrate wide variability in TCD findings, reflecting both genetic and environmental diversity. For instance, conditional and abnormal velocities are reported in 22.3% and 3.9% of PwSCD, respectively, in the Dominican Republic, 13% and 6.7%, respectively, in Jamaica, 6.5% and 1.2%, respectively, in Brazil, and 6.7% and 4.2%–7%, respectively, in India.[5-8] Despite these

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insights, Indian data remain sparse, especially regarding normative values for TCD velocities in tribal populations and the feasibility of TCD screening in resource-limited settings.

Our pilot study aims at evaluating the feasibility of TCD screening in a peripheral healthcare setting in Karnataka, establishing baseline TAMM velocities for the middle cerebral artery (MCA) and basilar artery (BA) in Indian Adivasi patients with SCD (SS and Sβ0 genotypes). We hypothesize that our findings will help in assessing the applicability of global TCD reference ranges in the Indian context and may provide preliminary data for region-specific stroke prevention guidelines. We strongly believe that our findings will address the evidence gaps, highlight TCD's potential as a cerebral risk stratification tool, and inform the development of targeted stroke prevention strategies for underserved SCD population in India.

Methods

This 3-year longitudinal prospective observational study, initiated in September 2024, investigated cerebral hemodynamics in predominantly Adivasi individuals with SCD enrolled in the population-based hemoglobinopathy registry of Chamarajanagara district, Karnataka. The registry provided a platform for integrated healthcare services, including quarterly health camps and annual evaluations through the state healthcare system. TCD was employed to establish baseline cerebral hemodynamics and assess cerebrovascular risk stratification.

Ethical approval was obtained, with routine care components exempted. Informed consent or assent was collected for research-specific procedures. Participants included individuals aged over 2 years with genotypically confirmed SCD (HbSS, HbS-thalassemia, or HbAS). TCD evaluations were performed during standardized health camps using Food and Drug Administration-approved TCD systems. A 2-MHz transducer insonated the M1 segment of MCA bilaterally (40–50 mm depth) and BA (70–80 mm depth via the transforaminal window), recording time-averaged mean maximum velocities (TAMMVs).

To account for the impact of anemia on TCD indices, hemoglobin (Hb) levels were measured from venous blood samples collected during routine evaluations. MCA TAMMVs were classified into risk categories based on global standards as follows: low risk (<170 cm/s), conditional risk (170–199 cm/s), and high risk (≥200 cm/s).[2] All data were anonymized, securely encrypted, and analyzed by certified neurosonologists to ensure accuracy and reliability.

In this ongoing longitudinal study, the primary objectives were to assess the feasibility of conducting TCD in peripheral areas and to determine the significance of TCD in assessing cerebral hemodynamics in Indian SCD patients. Furthermore, we aimed to establish TCD values specific to Indian SCD patients, which could assist in risk stratification for cerebral ischemia.

Statistical analysis

Statistical analyses (descriptives and frequencies) were performed using Jamovi version 2.6. *P*-values less than 0.05 were considered significant. Data were expressed as mean±SD.

Results

This preliminary analysis was based on data collected during the first camp organized at a peripheral site under an ongoing study. A total of 54 participants were recruited, including 37 individuals with SCD and 17 with sickle cell trait (SCT). Among them, 39 participants (27 with HbSS, three with HbSβ0 thalassemia, and nine with HbAS) underwent TCD evaluation.

Sixteen participants (six HbSS, one HbSβ0 thalassemia, and nine HbAS) were excluded from TCD assessment due to non-participation, primarily due to migration for employment and unavailability at the study site.

The demographic and hematological characteristics of the 39 participants who underwent TCD are summarized in Table 1, while the corresponding TCD parameters are presented in Table 2.

The SCD group had a younger mean age (18.62 ± 10.57 years) compared to the SCT group (24.8 ± 15.2 years) and a male predominance (62.2%), whereas the SCT group consisted of predominantly females (70.6%). The majority of the SCD group had the HbSS genotype (89.2%), with 45.9% requiring blood transfusions and 75.6% receiving hydroxyurea therapy.

Table 1: Demographic and clinical details of study participants with Sickle cell disease (SCD) or trait (SCT)

Variable	SCD (n=37)	SCT (n=17)
Age (years) (mean±SD)	18.62±10.57	24.8±15.2
Age range in years, n (%)		
≤5	2 (5.4)	1 (6)
6–17	17 (45.9)	6 (35)
18–40	16 (43.2)	6 (35)
≥40	2 (5.4)	4 (24)
Gender, n (%)		
Male	23 (62.2)	5 (29.4)
Female	14 (37.8)	12 (70.6)
Genotype, n (%)	HbSS=33 (89.2) HbSβ0=4 (10.8)	HbAS=17 (100)
Hemoglobin in g/L, mean±SD	9.49±1.55	11±2.1
Blood transfusion, n (%)		
Yes	17 (45.9)	Nil
No	20 (54.1)	
Hydroxyurea consumption, n (%)		
Yes	28 (75.6)	NA
No	9 (24.3)	
Stroke history	Nil	Nil
Pain crisis history, n (%)		
Yes	26 (70.3)	Nil
No	11 (29.7)	

SCD: sickle cell disease, SCT: sickle cell trait, SD: standard deviation, NA: Not applicable

Table 2: TCD parameters in MCA and BA and comparison between cases and controls

Artery	SCD (n=30)	SCT (n=17)	*P*-value
	Mean±SD	Mean±SD	SCD versus SCT
Mean MCA-PSV	90.89±22.06	78.631±18.7	0.140
Mean MCA-EDV	36.95±11.16	31.49±7.7	0.180
Mean MCA-PI	0.84±0.15	0.87±0.14	0.619
Mean MCA-MFV	54.24±15.67	47.21±10.61	0.217
Mean MCA-TAMM	59.68±15.6	57.68±14.8	0.734
BA-PSV	83.9±20.3	66.5±24.7	0.037
BA-EDV	37.6±12.4	24.3±11.5	0.007
BA-PI	0.81±0.21	0.86±0.2	0.546
BA-MFV	56.8±13.3	37.5±14.4	0.001
BA-TAMM	62.2±11.2	46.1±18	0.029

BA: basilar artery, EDV: end diastolic volume, IQR: interquartile range, MCA: middle cerebral artery, MFV: mean flow velocity, PI: pulsatility index, PSV: peak systolic velocity, SCD: sickle cell disease, SCT: sickle cell trait, SD: standard deviation, TAMM: time-averaged maximum mean, TCD: transcranial Doppler

Pain crises were reported in 70.3% of the SCD group, but were absent in the SCT group. Hb levels were significantly lower in the SCD group (9.49 ± 1.55 g/L) compared to the SCT group (11 ± 2.1 g/L). Notably, no history of stroke was reported in either group.

None of our SCD or SCT patients demonstrated elevated TAMMVs. TCD findings revealed significant differences in blood flow characteristics between SCD and SCT groups. For BA, SCD patients demonstrated significantly higher peak systolic velocity (PSV) (83.9 ± 20.3 vs. 66.5 ± 24.7 cm/s, $P = 0.037$), end diastolic velocity (EDV) (37.6 ± 12.4 vs. 24.3 ± 11.5 cm/s, $P = 0.007$), mean flow velocity (MFV) (56.8 ± 13.3 vs. 37.5 ± 14.4 cm/s, $P = 0.001$), and TAMMV (62.2 ± 11.2 vs. 46.1 ± 18 cm/s, $P = 0.029$) compared to SCT patients. However, pulsatility index (PI) values in BA were comparable between the groups, indicating no significant difference in vascular resistance ($P = 0.546$).

In contrast, parameters measured in MCA, including PSV (90.89 ± 22.06 vs. 78.63 ± 18.7 cm/s, $P = 0.140$), EDV (36.95 ± 11.16 vs. 31.49 ± 7.7 cm/s, $P = 0.180$), MFV (54.24 ± 15.67 vs. 47.21 ± 10.61 cm/s, $P = 0.217$), and TAMMV (59.68 ± 15.6 vs. 57.68 ± 14.8 cm/s, $P = 0.734$), showed no statistically significant differences between the groups. Similarly, PI values in MCA were not significantly different, reflecting preserved vascular resistance in both SCD and SCT patients ($P = 0.619$).

Discussion

The study demonstrates the feasibility of TCD screening in resource-limited, geographically isolated areas through expert collaboration, highlighting its potential for stroke risk assessment in underserved populations. In Karnataka, the HbS gene frequency is higher in tribal groups, with SCT prevalence being 0.8%–1.2% in the general population and 8%–10% in tribal communities. Homozygous SCD is rare in non-tribal populations (<1%), but reaches 6%–8% in tribal regions like Chamarajanagara due to genetic clustering.[1]

Indian TCD studies highlight regional variations in stroke risk among children with SCD. In South Gujarat, a study of 56 SCD children reported predominantly normal TCD results (89.3%, n = 50), with an average TAMMV of 127.59 ± 17.48 cm/s. Only 1.78% (n = 1) had abnormal velocities and 8.9% (n = 5) had conditional results, likely reflecting haplotype differences.[9] In contrast, Wardha (n = 50) reported higher mean velocities, with 10% (n = 5) of children showing velocities >200 cm/s, necessitating blood transfusions.[10] In Nagpur (n = 117), 23% (n = 27) had TAMMV outside the normal range, including 4.3% (n = 5) with abnormal velocities, 6.8% (n = 8) with conditional velocities, and 12% (n = 14) with low or unobtainable velocities. Stroke cases (n = 3, 2.6%) showed mixed TCD patterns, while seven children (6%) with isolated seizures had predominantly normal TAMMV (n = 5, 4.3%), with 1.7% (n = 2) showing low or conditional TAMMV.[11] A study from Raipur and Ahmedabad (n = 62) found 11% (n = 7) with abnormal velocities, and 9.6% (n = 6) had a history of stroke. Higher TAMMV was linked to elevated HbS levels, prior strokes, and transfusions.[8] These differences likely reflect genetic, environmental, and treatment factors, including the use of hydroxyurea. While Indian studies report a lower prevalence of abnormal velocities compared to global data, these findings emphasize the need for region-specific reference values and multicenter research to refine TCD protocols and stroke prevention strategies for diverse Indian SCD populations.[7-10]

None of the SCD patients in our study had a history of stroke or high/conditional TAMMV. But 22 of 30 (73.3%) showed unusually low MCA velocities (<70 Cm/S). Similarly, in Gujarat, 12% (N = 14) had low or unobtainable TAMMV, with one stroke case showing low values. These paradoxically low velocities, especially in the presence of lower Hb levels, highlight the need for further investigation. While higher TAMMVs are expected in patients with SCD and low Hb levels, the observed low values remain unexplained. While lower TCD flow velocities might reflect severe steno-occlusive disease warranting advanced imaging,[8] It appears unlikely

in our participants since the PI values were normal. Indian studies predominantly report normal TAMMVs, particularly in hydroxyurea-treated children, as seen in our cohort, where three fourths were on hydroxyurea; however, regional variations – normal in south Gujarat and Raipur versus higher abnormal and conditional in Nagpur and Wardha – may reflect differences in phenotypes, haplotypes, hydroxyurea use, and community composition, underscoring the need for region-specific TCD reference values and multicentric studies to optimize stroke risk assessment in India's diverse SCD populations.

Global TCD studies highlight variations in stroke risk and cerebral hemodynamics in SCD, influenced by clinical, hematological, and regional factors. A cross-sectional study of 150 Congolese children with SS reported 14% at risk of stroke, with 4% showing pathological TCD velocities and 10% at conditional risk with mean MCA velocity of 114.0 cm/s; TCD risk was associated with white blood cells (WBC), Hb, hemoatocrit (HCT).[12] In another cohort of 770 children aged 2–17 years, 78% were at low risk, 17% at conditional risk, and 0.4% at high risk, with 2.2% developing neurologic symptoms during follow-up.[13] The BRAIN SAFE-II trial on 264 American children initiating hydroxyurea noted four strokes despite normal or conditional TCD results, implicating factors like low HbF or acute complications.[14] An Iraqi study on 1173 SCD patients reported a 1.91% prevalence of conditional TCD, with mean HbF of 18.2% and HbS of 70.2%, though stroke outcomes were not reported.[15] These studies provide support to our findings and further reinforce our hypothesis about regional genotype–phenotype differences.

The stroke risk in Indian SCD populations (2.6%–2.9%) is lower than global rates (up to 11%), despite a high prevalence of VOCs, suggesting distinct cerebral hemodynamics. Factors like hydroxyurea use, phenotypic variability, and diverse clinical manifestations across Indian subpopulations require further exploration. The applicability of Stroke Prevention Trial in Sickle Cell Anemia (STOP) trial thresholds to Indian cohorts remains unclear, necessitating multicentric studies to evaluate regional, genetic, and phenotypic variations. These efforts are vital to refine stroke risk stratification and develop tailored neurologic management strategies for Indian SCD patients.

Limitations and recommendations for future research

Our preliminary findings are subject to certain limitations. Data were collected from an SCD cohort in remote, resource-limited areas using a camp-based approach, which may have influenced our observations. These results represent the first ever screening camp conducted at a peripheral site, where neuroimaging was not feasible. However, neuroimaging will be incorporated in subsequent phases of the study to validate TCD findings and assess brain parenchymal changes in Indian SCD patients. While the cross-sectional TCD data provide useful insights, longitudinal follow-up is essential to better understand cerebral hemodynamics in this population. The small sample size may also account for observed differences between SCD and SCT groups. We strongly recommend larger multicenter studies across India to generate robust, population-specific reference data. Although TCD findings were not corroborated with imaging in this phase, our data did not suggest a high likelihood of severe steno-occlusive disease in major intracranial arteries.

Conclusion

The present study demonstrates that TCD screening is feasible for stroke risk assessment in resource-restricted Indian settings, revealing distinct cerebral hemodynamic profiles in patients with SCD compared to healthy controls. Despite a high burden of VOCs, the relatively lower prevalence of abnormal TCD velocities and stroke is an interesting and unexplained phenomenon. Our findings emphasize the need for multicentric research across diverse Indian cohorts to establish region-specific TCD reference values and tailored stroke prevention protocols.

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Conflicts of interest

There are no conflicts of interest.

References

1. Rao P, Raj EA, Natesan S, Gudi N. Prevalence of Sickle cell disease, Sickle cell trait and HBS-beta-thalassemia in India: A systematic review and Meta-analysis. Clin Epidemiol Glob Health 2024;28:101678.
2. Adams RJ, McKie VC, Hsu L, Files B, Vichinsky E, Pegelow C, et al. Prevention of a first stroke by transfusions in children with sickle cell anemia and abnormal results on transcranial Doppler ultrasonography. N Engl J Med 1998;339:5-11.
3. DeBaun MR, Jordan LC, King AA, Schatz J, Vichinsky E, Fox CK, et al. American Society of Hematology 2020 guidelines for sickle cell disease: Prevention, diagnosis, and treatment of cerebrovascular disease in children and adults. Blood Adv 2020;4:1554-88.
4. Desnos L, Allaert F, Etienne-Julan M, Blanchet-Deverly A. Study of-maximum systolic velocities and mean maximum velocities of skull base arteries recorded with transcranial Doppler in adult sickle cell patients without neurovascular complication. J Med Vasc 2019;44:249-59.
5. Bhattacharya P, Sarmah D, Dave KR, Goswami A, Watanabe M, Wang X, et al. Stroke and stroke prevention in sickle cell anemia in developed and selected developing countries. J Neurol Sci 2021;427:117510.
6. Rankine-Mullings A, Reid M, Soares D, Taylor-Bryan C, Wisdom-Phipps M, Aldred K, et al. Hydroxycarbamide treatment reduces transcranial Doppler velocity in the absence of transfusion support in children with sickle cell anaemia, elevated transcranial Doppler velocity, and cerebral vasculopathy: The EXTEND trial. Br J Haematol 2021;195:612-20.
7. Jain D, Ganesan K, Sahota S, Darbari DS, Krishnamurti L, Kirkham FJ. Transcranial Doppler screening in children with sickle cell anemia is feasible in central India and reveals high risk of stroke. Blood 2019;134(Suppl 1):2279.

8. Gajjar B, Sharma S, Khan E, Sharma P, Jain P, Goel V, et al. Cerebral hemodynamics in children with sickle cell disease in India: An observational cohort study. Medicine (United States) 2022;101:E29882.
9. Desai EJ, Patel D, Shastri MD, Mishra S. Transcranial doppler screening in children with sickle cell disease of south gujarat population. Natl J Community Med 2021;12:380-3.
10. Singhal RP, Bansal H, Jain M, Lakhar B, Jain S. Sickle children vs normal children: A transcranial and extracranial doppler stud. Int J Anat Res 2015;3:856-60.
11. Jain D, Arjunan A, Sarathi V, Jain H, Bhandarwar A, Vuga M, et al. Clinical events in a large prospective cohort of children with sickle cell disease in Nagpur, India: Evidence against a milder clinical phenotype in India. Pediatr Blood Cancer 2016;63:1814-21.
12. Kazadi GT, Mbuyi DM, Kitenge R, Mpaka S, Gini JLET, Ngiyulu R, et al. Transcranial Doppler in 150 Congolese children with sickle cell disease. Front Stroke 2024;3:1384767.
13. O'Brien NF, Moons P, Johnson H, Tshimanga T, Musungufu DA, Ekandji RT, et al. Transcranial Doppler ultrasound velocities in a population of unstudied African children with sickle cell anemia. eJHaem 2024;5:3-10.
14. Naggayi SK, Kalibala D, Mboizi V, Ssenkusu J, Jin Z, Rosano C, et al. Neurocognitive Improvement with Hydroxyurea Therapy in Children with Sickle Cell Anemia in Uganda: Analysis from the Completed 30-Month BRAIN Safe II Trial. Blood 2024 Nov 5;144:543.
15. Basim Alhijaj AA, Yeser WJ, Othafa HM. Transcranial Doppler in screening of sickle cell disease in Basrah: A cross- sectional descriptive study. Front Biomed Technol 2025;12:229-34.