EXTRACRANIAL CAROTID DOPPLER STUDY IN CHILDREN WITH SICKLE CELL DISEASE IN STEADY STATE: A CROSS-SECTIONAL STUDY

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ABSTRACT:

Aim: Evaluation of the extracranial carotid Doppler blood flow velocities in Sickle cell disease children.

Methods: A Cross-sectional study for 2 years duration included all the patients from 4 to 17 years of the age group of sickle cell disease. Extracranial carotid Doppler study is performed over bilateral common carotid arteries, external carotid arteries, internal carotid arteries, and vertebral arteries. Extracranial carotid Doppler blood flow velocities were noted in all arteries and categorized the patients into high risk, borderline risk, and normal velocity depending upon reference values for the risk for cerebrovascular accidents according to STOP trial. Also, a correlation of raised velocity with blood transfusion, hydroxyurea, and CNS symptoms were noted. The total sample size was 94. Data were analysed by chi-square test.

Results: Of the total 94 sickle cell disease children, only 3 children showed increased carotid Doppler blood flow velocity. 2 (2.12%) out of 44 SS pattern patients who were not on hydroxyurea therapy showed increased extracranial carotid doppler blood flow velocities. 1 (1.06%) out of 45 AS pattern patients who were not on hydroxyurea therapy showed increased blood flow velocities. 2(2.12%) out of 26 SS pattern patients who never received a blood transfusion showed increased blood flow velocities.1(1.06%) out of 44 AS pattern patients who never received blood transfusion had increased blood flow velocities. 2 (2.12%) out of 44 SS patients who had CNS symptoms showed increased blood flow velocities. 1 (1.06%) out of 45 AS patients who had CNS symptoms showed increased blood flow velocities.

Conclusion: Extracranial carotid Doppler blood flow velocities are not associated with blood transfusion, hydroxyurea therapy, and the presence of CNS symptoms.

Keywords: STOP trial, extracranial carotid Doppler, sickle cell disease.

INTRODUCTION:

Sickle cell disease (SCD) is a genetic disorder presenting as an autosomal recessive trait. It is usually a consequence of deformity in hemoglobin irrespective of synthesis defect.[1] It refers to a group of hemoglobinopathies that comprises gene mutation encoding the hemoglobin beta subunit.[2] It is the replacement of glutamine by valine in the beta subunit of globin at its sixth position. This is the usual sickle cell mutation found.[3] Mendelian genetics comes into major role play during this mutation transmission and is also passed on to generations in an autosomal codominant manner.[4-5]

Sickle cell anemia has two major components: Haemolysis and Vaso-occlusive crises[6]

Basically, beta-globin malformations predispose sickle hemoglobin (HbS) molecules in rigid, and long polymers in the deoxygenation state.[7] The process of sickling makes it round and circular initially, where sickle RBCs vary from normal shape and the abnormal crescentic form.[5] However, with time, these changes become irreversible, and the sickle RBCs acquire a non-changeable sickle shape. This further increases the threat of haemolysis and Vaso-occlusive crisis.[8-9] All types of SCD have the same pathophysiological process resulting in HbS component polymerization.[8]

Stroke in SCD is preventable if Doppler studies for carotids are performed periodically. Understanding the importance of Doppler studies, we had planned this study to observe extracranial carotid Doppler blood flow velocities in SCD.

AIM AND OBJECTIVES

AIM: To evaluate the extracranial carotid Doppler blood flow velocities in SCD children

OBJECTIVES: Primary objective of the study is to analyses extracranial carotid Doppler blood flow velocities in SCD children in a steady state. Association of variation of blood flow velocities with the type of SCD, to observe the correlation of blood transfusion, hydroxyurea therapy, and CNS symptoms with extracranial carotid blood flow velocities.

METHODOLOGY

Institutional Ethics Committee (IEC) approved the protocol for our study. This was a cross-sectional study done in a tertiary care hospital. The duration of the study was of 2 years i.e., from September 2019 to August 2021. The study was performed in the Paediatrics Department of a tertiary care hospital located in Central India. All patients from 4 to 17 years of the age group of sickle cell disease at steady state visiting the Out-Patient Department (OPD) of the Paediatrics department over a period of 2 years were included in the study.

INCLUSION CRITERIA:

1. Patients aged between 4-17 years of either sex willing to enroll in the study.
2. All sickle cell children in their steady state including SS, AS, and sickle β Thalassemia as diagnosed as per Hb electrophoresis by High-performance liquid chromatography (HPLC) method.

EXCLUSION CRITERIA

1. Patients who had participated in other trials in the period of 30 days before our study
2. Patients with co-morbid conditions which might confound the study findings.
3. Patients with a history of head injury, convulsion, or perinatal asphyxia.

DATA COLLECTION: Detailed demographic data with respect to name, age, detailed address, and education. Data were entered from the case record form in an excel sheet. Informed consent was taken from every patient before enrolling in the study by giving knowledge about the nature of the study as per the patient information sheet. The patient was evaluated with clinical history and examination of confirmed cases of sickle cell disease by hemoglobin electrophoresis. The patient was shifted to the USG examination room for color doppler of extracranial carotid arteries and placed in a supine position with the extension of the neck for the study of extracranial carotid doppler. USG Carotid doppler machine - SAMSUNG RS 80 A PROBE Frequency- 9 MHz was used. The site of examination was exposed, cleaned and extracranial carotid arteries by doppler, and velocity readings were noted. Bilateral Common carotid arteries, external carotid arteries, internal carotid arteries, and vertebral arteries were examined. The examination was done by a single ultrasonologist to prevent study variation. The calculated sample size was 94.

STATISTICAL ANALYSIS: Data was expressed as a percentage and mean ± S.D. Kolmogorove-Smirnove analysis was implemented for checking the linearity of the data using MS Excel for collecting the data. The significance of the difference between the frequency distribution of the data was analysed by the chi-square test. P value <0.05 was reflected as statistically significant. SPSS© for windows™ Vs 17, IBM™ Corp NY, and Microsoft excel™ 2007, Microsoft® Inc USA was used to perform the statistical analysis.

RESULTS:

The total number of children with sickle cell disease included in this study was 94. The distribution of patients as per the type of sickle cell anemia is given in table 1. Out of the total 94 patients, 44 (46.8%) patients were on hydroxyurea therapy. There were 21 (22.3%) patients with SCD who has given a blood transfusion. There were 9 (9.4%) patients who had CNS symptoms. Maximum patients were in the 10-15 years age group.

Out of the total 94 patients. 3 (3.19%) had borderline increased extracranial carotid Doppler blood flow velocities (table 2).AS pattern patient and one of the 2 SS pattern patients who had increased blood flow velocity showed raised velocity in RCCA. Other SS pattern patients had increased velocity in LCCA. The maximum velocity in RCCA was 199 cm/s, minimum velocity in RCCA was 64 cm/s. The maximum velocity in LCCA was 188cm/s. The minimal velocity in LCCA was 68cm/s. The mean blood flow velocities were 111.07 cm/s in both right and left common carotids

There is no statistically significant correlation between increased extracranial carotid Doppler blood flow velocities with hydroxyurea therapy. Only 2 (2.12%) out of 44 SS patients who had CNS symptoms showed increased blood flow velocities. Only 1 (1.06%) out of 45 AS patients who had CNS symptoms showed increased blood flow velocities. Hence,

there was no statistically significant correlation between increased blood flow velocity and the presence of CNS symptoms.

Table1.Distribution of patients according to sickle cell disease types. (N=94)

		Frequency	**Percentage (%)**
Type of sickle cell disease	SS	44	46.8
	AS	45	47.9
	Sβ-THAL	5	5.3
	Total	**94**	

Table 2: Distribution of Extracranial Carotid Doppler Blood Flow Velocities in various Types of Sickle cell disease. (N=94)

Type of sickle cell disease	**Standard risk <170 cm /sec**	**Borderline risk 170-200 cm /sec**	**High risk >200 cm/sec**
SS	42 (44.6%)	2 (2.12%)	0
AS	44 (46.8%)	1 (1.06%)	0
SICKLE βTHAL	5 (5.3%)	0	0
TOTAL	**91(96.8%)**	**3 (3.19%)**	**0**

DISCUSSION

In our study, we included 94 patients in the 4 to 17 years age group for the duration of two years. 44 (46.8%) were on hydroxyurea therapy.21 (22.3%) received blood transfusions. Adams et al (2005) performed a study on SCD children with a high risk of stroke on a transcranial Doppler screening (TCD) examination. Out of that 38 patients, 19 patients received transfusions without phlebotomy, 8 patients received transfusions by more than two methods, 7 patients received automated erythrocyte apheresis and 4 patients received manual exchanges.[10] Fullerton HJ studied that periodic blood transfusion in cases of TCDs abnormalities decreases the risk of stroke by 90% and reduces the incidence of overt cerebrovascular disease.[4]

In our study, 3 (3.19%) out of 94 subjects had borderline increased extracranial carotid Doppler blood flow velocities. Of them, 2 (2.12%) had SS and 1 (1.06%) had AS pattern. Goldstein LB 2003 found no sign of extracranial carotid disease in children with SCA.[5] Deane 2010 demonstrated an increased risk of stroke in children by Doppler ultrasound of the extracranial ICA which was an important useful screening tool compared to routine TCD. The advantages of this study were non-invasive, quick, and cheap to perform, and did not require any anesthesia or sedation. Hence, they recommended extracranial examination to rule out stenosis of the ICA, and tortuosity and to measure PSV.[11] Gaikwad et al. (2017), performed transcranial carotid Doppler in children of 2-15 years of age group with SCA. A

total of 64 patients were enrolled, and transcranial velocity in the Internal carotid artery between 170-200cm/s was present in 37.5% of patients and 6.25% of patients had TCV of >200cm/s.[16]

AS pattern patient and one of the 2 SS pattern patients who had increased flow velocity showed increased velocity in RCCA. Other SS pattern patients had increased velocity in LCCA. The maximum velocity in RCCA was 199 cm/s & in LCCA was 188cm/s, however minimum velocity in RCCA was 64 cm/s. & in LCCA was 68cm/s. The mean blood flow velocities were 111.07 cm/s in both right and left common carotids. Deane 2010 found that regular transcranial Doppler investigations were important in the treatment of children with sickle cell anemia, & identifying those at high risk of preventable stroke.[25] Salama et al. 2020, studied a cross-sectional study on TCD velocities among SCDs in a steady state. As per the Stroke Prevention Trial in Sickle Cell Anaemia (STOP) protocol, all patients underwent TCD velocity examination. TCD velocities were compared in Hb S/β-thalassemia versus SS cases. Hemolytic indicators were associated significantly with TCD velocities among Hb S/β-thal patients.[13] Deane et al. (2010)**,** studied the value of TCD screening for extracranial internal carotid artery disease. In normal vessels, the left and right-sided velocities were not shown any significant differences, and the highest value was used for further studies. The median PSV velocity was 148cm/s (5^{th} centile was 84, 95^{th} centile was 236). parameters like younger, leucocytosis, age, and higher hemolytic rates were correlated with Higher velocities.[11] Pawlak et al (2009) examined extracranial internal carotid artery velocities among 56 SCA children and found that mean PSVs of left and right extracranial ICA were 113 cm/s and 121cm/s respectively.[14] Bhattacharya et al 2007 demonstrated sickle cell disease cases having extracranial internal carotid artery stenosis. All stenosis was evaluated by MRA done due to acute stroke noted in 3 cases and TCD velocities increased in one case.[15]

In contrast, to the present study, Ismail et al (2019) studied 100 children of SCA at steady state, & observed that the highest TAMMV was in the MCA followed by ACA, PCA, and t ICA.[16] In our study 2 out of 44 SS and 1 out of 45 AS pattern patients who were not on hydroxyurea, who never received blood transfusion therapy, and with CNS symptoms showed increased extracranial carotid doppler blood flow velocities. There was no statistically significant correlation between increased extracranial blood flow velocity and Hydroxyurea therapy. Similar to our findings, Sherri A. Zimmerman, et al (2007) studied 59 children with baseline transcranial Doppler measurements. 37 patients with increased blood flow velocities were enrolled to review the effect of hydroxyurea and they found that hydroxyurea can significantly decrease elevated blood flow velocities.[16] In contrast to our study, Gaikwad et al. (2017) studied Carotid Doppler velocities in children aged 2-15 years with Sickle cell anemia. A total of 64 patients were enrolled, Patients who were on Hydroxyurea therapy had reduced transcranial velocities as compared to those who were not on therapy.[12]

CONCLUSION

There was no statistically significant correlation between increased extracranial blood flow velocity and with no hydroxyurea therapy (p-0.386), Blood Transfusion therapy (p-0.456), and presence of CNS symptoms (p-0.45)

LIMITATIONS:

Because of the small sample size of the study, it was not possible to correlate the effect of hydroxyurea therapy, blood transfusion, and CNS symptoms with increased extracranial carotid doppler blood flow velocities. In order to draw a conclusion, further similar studies with a larger sample size are needed.

In the present study, extracranial carotid doppler flow rates of the right and left side, CCA, ICA, ECA, and VA were studied. We could not trace anterior and posterior cerebral arteries and communicating arteries which can be possible only in transcranial doppler study. Hence for better assessment and results, we have to include transcranial doppler along with an extracranial doppler study.

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CONFLICT OF INTEREST- The authors declare that they have no conflict of interest.

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