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Research Paper

Study of Mean Blood Flow Velocities in Different Cerebral Vessels Using Transcranial Doppler Ultrasonography in Children With Sickle Cell Disease

Medical Science

KEYWORDS : Sickle Cell Disease (SCD), Transcranial Doppler (TCD), Time-Averaged Maximum Mean Velocities (TAMV), STOP (Stroke Prevention Trial in Sickle Cell Anemia).

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ABSTRACT

Introduction : The prevalence of SCD in the population of Chhattisgarh state is about 10 to 15% of which about 1 to 1.27% are likely to be sufferers and the rest carriers. Prevalence is more in certain communities of Chhattisgarh like Sahu, Kurmi, Nayak, Patel and some tribal populations. Stroke is a serious complication of sickle cell disease and can be predicted by using transcranial Doppler.

Material and methods : This prospective cross sectional observational study, all children were undergone transcranial Doppler examinations following the criteria of the STOP (Stroke Prevention Trial in Sickle Cell Anemia) study. The time-averaged maximum mean velocities (TAMV) were determined in various cranial arteries. After data collecting, the statistically analyse.

Conclusion : SCD SS children had higher mean velocity than controls and the difference was statistically significant. Mean velocity of intracranial arteries didn't show significant changes with age.

Introduction

Chhattisgarh is situated in Middle East India with a population of approximately 21 million of whom 32% are tribal in origin. Sickle Cell disorders are a group of inherited genetic disorders and a major public health problem in Chhattisgarh therefore this area is popularly called sickle belt due to high prevalence of this condition[1,2].

sickle cell anemia (SCA) the form of the disease that occurs in homozygous of hemoglobin S (HbSS) heterozygous (HbAS), as well as pathological conditions caused by combinations of the hemoglobin S gene with other hereditary hemoglobin disorders such as sickle cell SC disease, HbS/ß+ thalassemia and HbS/ß0 thalassemia[3,4].

The prevalence of SCD in the population of Chhattisgarh is about 10 to 15% of which about 1 to 1.27% are likely to be sufferers and the rest carriers. About 35 lacs of carriers and 2.5 lacs of sufferers are expected to exist in Chhattisgarh. Prevalence is more in certain communities of chhattisgarh like Sahu, Kurmi, Nayak, Patel and some tribal populations [5,6,7].

Stroke is a serious complication of sickle cell disease with frequency of 0.61 per 100 patients per year[8]. Transcranial Doppler ultrasonography (TCD) helps to identify children with sickle cell disease (SCD) who are at an increased risk of stroke, making primary stroke prevention a reality. TCD should be used for primary prevention of strokes in SCD patients, regardless of the genotype of the disease[9].

This study was done out of curiosity to see whether our patients differed from patients elsewhere. The objective of this study was to measure mean flow velocity in different vessels in homozygous sickle cell patients using transcranial Doppler study and its variation over age and gender in Chhattisgarhi population and to correlate mean velocity with headache or stroke if any.

Methods

This prospective cross sectional observational study conducted in the Department of Paediatrics and Radiodiagnosis, Dr.B.R.Ambedkar Memorial Hospital, Raipur (C.G.) in Children between 2 to 14 yrs diagnosed as sickle cell disease SCD SS (by hemoglobin electrophoresis) and attending sickle cell clinic were included in study. Age and sex matched normal children attending Pediatric OPD for minor illnesses were used as controls. Study was approved by ethical and scientific committee. Informed consent was obtained from all the guardian or caregivers regarding technique and benefits of routine transcranial Doppler.

Those sickle cell children excluded from study that were below age 2 years and above 14 years, recent blood transfusions, painful crisis, fever, infections, history of major head injury, history of seizure disorder requiring anticonvulsant therapy, history of prenatal or perinatal hypoxic, on Hydroxyurea therapy.

All children were undergone transcranial Doppler examinations in quiet and wakeful state by Doppler using apparatus with a 2 MHz transducer and following the criteria of the STOP (Stroke Prevention Trial in Sickle Cell Anemia) study. the time-averaged maximum mean velocities(TAMV) were determined every 2 mm along the bilateral anterior cerebral arteries, middle cerebral arteries, bilateral ophthalmic arteries and basilar artery using appropriate windows - Trans temporal (MCA,ACA), Trans orbital (ophthalmic artery), sub occipital (Basilar artery) [10].

TCD studies has been performed in steady state i.e crises free period, at least 3 weeks since last clinical event and 3 months or more since last blood transfusion, before the start of new clinical event. The highest value was taken as the time-averaged maximum mean velocity for each patient.

Statistics

After data collecting, the statistical software of SPSS v.17 was used to analyze data. Descriptive statistics such as average, standard deviation and percent were used to data description and in inferential statistics section, T-test was used.

Result

Total numbers of SCD SS patients (cases) in this study were 104 and numbers of normal subjects (control) were 27. Among the cases the total number of males were 73 (70%) and females were 31 (30%). male female ratio was 2.35% .Among the control group the total number of males were 18 (67%) and total number of females were 9(33%). male female ratio was 2.00%.

Table 1 showed Distribution of mean velocity of intracranial vessels in SCD SS (n=104) and control group (n=27). In the SCD SS group (cases) mean velocity was in the normal range (<170 cm/sec) in all patients. In control group also mean velocity was in the normal range (<170cm/sec) in all subjects.

Table 1 Mean velocity of intracranial vessels in SCD SS (n=104) & control group(n=27)

	SCD SS PATIENTS (N=104)		CONTROL GROUP(N=27)	
MEAN VELOCITY (CM/SEC.)	No.	%	No.	%
NORMAL (<170)	104	100%	27	100%
CONDITIONAL (170-200)	0	0%	0	0%
HIGH RISK (>200)	0	0%	0	0%

Table 2 showed Comparison of mean blood flow velocities of different intracranial vessels between SCD SS patients (n=104) and normal subjects (control group) (n=27). mean blood flow velocities of intracranial blood vessels in SCD SS patients n=104(cases) were as follows – mean ± SEM, 95%CI-RT MCA -89.62 ± 2.49, 95%CI-84.68-94.56 , RT ACA - 69.66 ±2.61, 95%CI-64.48-74.84, RT OPTH-33.96 ± 1.80, 95%CI-30.39-37.53,LT MCA - 90.82 ±2.48 , 95%CI-85.90-95.74, LT ACA-75.46±2.21, 95%CI-71.08-79.84, LT OPTH-35.24 ± 1.82, 95%CI-31.63-38.85 , basilar artery - 82.14 ± 2.29 , 95%CI-77.61-86.67. Mean blood flow velocities of intracranial blood vessels in control group n=27 were as follows – mean ± SD (confidence level) RT MCA-72.65 ±2.96, 95%CI-66.56-78.74,RT ACA - 52.97 ±4.25, 95%CI- 44.23-61.71, RT OPTH-14.33 ± 0.77, 95%CI-12.75-15.91, LT MCA - 70.89 ±2.59, 95%CI-66.57-76.21,LT ACA - 49.86 ±2.92,95%CI-43.86-55.86,LT OPTH - 14.66 ±0.65, 95%CI-13.31-16.01, basilar artery - 61.39 ±2.22, 95%CI-56.83-65.95. There was statistically significant difference (p value is less than 0.05) in mean blood flow velocity between SCD SS and control group.

Table 2 showed Comparison of mean velocity between male (n=73) and female (n=31) in SCD SS patients. Mean velocity of left ophthalmic artery was higher in females as compared to males and the difference was significant statistically (P value is less than 0.05).

Table 2 Comparison of mean blood flow velocities of intracranial vessels between SCD SS patients (n=104) and normal subjects (control group) (n=27)

	SCD SS (n=104)		CONTROL GROUP (n=27)			
	MEAN ± SEM	95%CI	MEAN ±SEM	95%CI	Z VALUE	P VALUE
RT MCA	89.62 ± 2.49	84.68-94.56	72.65 ± 2.96	66.56-78.74	4.38	<0.000*
RT ACA	69.66 ± 2.61	64.48-74.84	52.97 ± 4.25	44.23-61.71	3.34	<0.000*
RT OPTH	33.96 ± 1.80	30.39-37.53	14.33 ± 0.77	12.75-15.91	10.03	<0.000*
LT MCA	90.82 ± 2.48	85.90-95.74	70.89 ± 2.59	66.57-76.21	5.56	<0.000*
LT ACA	75.46 ± 2.21	71.08-79.84	49.86 ± 2.92	43.86-55.86	6.99	<0.000*
LT OPTH	35.24 ± 1.82	31.63-38.85	14.66 ± 0.65	13.31-16.01	10.64	<0.000*
BASILAR	82.14 ± 2.29	77.61-86.67	61.39 ± 2.22	56.83-65.95	6.51	<0.000*

Table 3 showed comparison of mean blood flow velocities of intracranial vessels between male SCD SS patients (n=73) and normal male subjects controls (n=18). Among SCD SS male (n=73)patients mean blood flow velocity was as follows -MEAN±SEM, 95%CI- RT MCA -88.71 ±3.07, 95%CI-82.71-94.71, RT ACA- 67.44±3.12, 95%CI-61.33-73.55, RT OPTH-33.96 ±1.80, 95%CI-30.39-37.53, LT MCA -89.57 ± 3.12, 95%CI-83.45-95.69 , LT ACA - 73.72 ± 2.73, 95%CI-68.37-79.07 , LT OPTH- 32.55 ± 1.83, 95%CI-28.96-36.14, basilar -81.98 ± 2.87, 95%CI-76.36-81.98 Among control normal male (n=18) patients mean blood flow velocity was as follows - MEAN±SEM, 95%CI-RT MCA -68.00 ± 3.54, 95CI%-61.07-74.93, RT ACA-51.59 ±3.36, 95%CI-45.01-58.17, RT OPTH-14.65 ±0.95, 95%CI-12.80-16.50 , LT MCA -67.13 ± 3.01, 95%CI-61.23-73.03 , LT ACA - 46.31 ± 2.58, 95%CI-41.25-51.37, LT OPTH- 14.86±0.82, 95%CI-13.25-16.47, basilar artery -57.96 ±2.39, 95%CI-53.28-62.64.

There was statistically significant difference (p value is less than 0.05) in mean blood flow velocity between male SCD SS patients and male normal subjects.

Table 3 comparison of mean blood flow velocities of intracranial vessels between SCD SS female patients (n=31) and normal female subjects (n=9). mean blood flow velocities of intracranial vessels in SCD SS Female patients (n= 31) was as follows- MEAN±SEM, 95%CI- RT MCA-91.77 ± 4.24, 95%CI-83.46-100.08, RT ACA-74.87±4.72,n 95%CI-65.62-84.12, RT OPTH -39.54±4.00, 95%CI-31.68-47.40, LT MCA-93.77 ±3.94, 95%CI-86.05-101.49, LT ACA79.55 ±3.65, 95%CI-72.40-86.70, LT OPTH-41.60 ±4.16, 95%CI-33.45-49.75, Basilar 82.50 ±3.70, 95%CI-75.26-89.74.

mean blood flow velocities of intracranial vessels in normal female subjects (n= 9) was as follows- MEAN±SEM, 95%CI- RT MCA- 81.94 ±4.00, 95%CI-74.09-89.79 ,RT ACA-55.71 ±11.26, 95%CI-33.63-77.79 ,RT OPTH -13.68±1.36, 95%CI-11.02-16.34, LT MCA-78.4 ±4.01, 95%CI-70.54-86.26 ,LT ACA- 56.96 ±6.73, 95%CI-43.78-70.14, LT OPTH-14.24 ±1.13, 95%CI-12.02-16.46 ,Basilar 68.23 ±3.86, 95%CI-60.67-75.79.

There was statistically significant difference in mean velocity between female SCD SS and control group in RT OPTH ,LT MCA, LT ACA, LT OPTH , basilar artery (p value is less than 0.05)

Table 4 Comparison of mean blood flow velocities of intracranial vessels SCD SS patients

	Male						Female					
	SCD SS (n=73)		CONTROL(n=18)				SCD SS(n=31)		CONTROL (n=9)			
	MEAN ±SEM (n=73)	95% CI	MEAN ±SEM (n=18)	95% CL	Z value	P value	MEAN ± SEM	95% CI	MEAN ±SD SE	95% CI	Z value	P value
RT MCA	88.71 ± 3.07	82.71-94.71	68.00± 3.54	61.07-74.93	4.42	<0.000*	91.77 ± 4.24	83.46-100.08	81.94 ± 4.00	74.09-89.79	1.68	0.092

	Male						Female					
	SCD SS (n=73)		CONTROL(n=18)				SCD SS(n=31)		CONTROL (n=9)			
RT ACA	67.44 ±3.12	61.33-73.55	51.59 ±3.36	45.01-58.17	3.46	<0.000*	74.87 ±4.72	65.62-84.12	55.71 ± 11.26	33.63-77.79	1.41	0.156
RT OPTH	33.96 ±1.80	30.39-37.53	14.65 ±0.95	12.80-16.50	8.04	<0.000*	39.54 ±4.00	31.68-47.40	13.68 ± 1.36	11.02-16.34	6.11	0.000*
LT MCA	89.57 ±3.12	83.45-95.69	67.13 ± 3.01	61.23-73.03	5.17	<0.000*	93.77 ±3.94	86.05-101.49	78.4 ± 4.01	70.54-86.26	2.73	0.006*
LT ACA	73.72 ±2.73	68.37-79.07	46.31 ±2.58	41.25-51.37	7.29	<0.000*	79.55 ±3.65	72.40-86.70	56.96 ± 6.73	43.78-70.14	2.95	0.003*
LT OPTH	32.55 ±1.83	28.96-36.14	14.86 ±0.82	13.25-16.47	8.81	<0.000*	41.60 ±4.16	33.45-49.75	14.24± 1.13	12.02-16.46	6.98	0.000*
BASILAR	81.98 ±2.87	76.36-81.98	57.96 ± 2.39	53.28-62.64	6.43	<0.000*	82.50 ± 3.70	75.26-89.74	68.23 ± 3.86	60.67-75.79	2.66	0.007*

Table 5 show Correlation between mean age and mean velocity of different intracranial arteries is not significant statistically (p value is more than 0.05) in SCD SS patients. (P value <0.05 is significant)

Discussion

Stroke is the most severe complication in homozygous (HbSS) sickle cell disease (SCD) patients, most frequently results from occlusion or diminution of cerebral blood flow of major intracranial arteries. Transcranial Doppler ultrasonography (TCD) has been used to measure blood flow velocity in the intracranial arteries of the circle of Willis, including the internal carotid artery (ICA) and the middle cerebral artery (MCA). Focal elevation of velocity, by means of TCD measurement, usually indicates arterial stenosis because flow velocity is directly related to cerebral blood flow and inversely related to arterial diameter[11, 12].

Transcranial Doppler is used early diagnosis of the risk of stroke in sickle cell disease. If the velocity of cerebral blood flow increases in patients, they require transfusion to prevent a stroke. Many factors can affect the cerebral blood flow velocities (CBFV) including age, sex, body temperature, blood viscosity, arterial blood pressure, obesity, metabolic state, cardiac function, carbon dioxide tension, oxygen tension, intracranial pressure, some drugs, smoking and alcohol.

Narrowing of intracranial vessels in SCD progress for months or years before cerebral symptoms develop and so there is an opportunity to detect vascular narrowing before cerebral lesions develop. As per STOP study velocities were considered to as Normal - < 170cm/sec. Conditional – 170-199c m/sec and High or abnormal- > 200cm/sec. Flow velocities of 200 cm/sec in the middle cerebral or the internal carotid arteries has been reported to be associated with 40% risk of developing a stroke while flow velocities of <170 cm/sec and 170–199 cm/sec are associated with a stroke-risk of 2% and 7%, respectively[24, 25]. The time averaged maximum mean velocity (TAMM) was measured in seven arteries on both sides to categorize the study as either normal, conditional, abnormal. Recordings from both middle cerebral (MCA) and internal carotid (distal portion or bifurcation) (ICA) arteries were required for a TCD exam to be considered adequate[15].

Table 6 showed comparison of various studies findings with where in present study the mean velocity was in the normal range (<170 cm/sec) in all patients in both groups.

Table 6 Comparison of various study from present study

	Mean velocity(cm/sec)	
	Conditional(170-199)	High Risk(>200
Present Study	0%	0%
Melo,et al 2005	11.7%	0.0%
Park, et al 2006	14.3%	2.6%
Silva et al,2008	10.4%	4.6%
Pavlakis sq,et al [20]	2%	0 %
Mary Hokazonoi, et al [22]	8.1%	1.6%
Ana Claudia, et al [21]	6.5%	1.2%
Mohammad Ali, et al [17]	4.76%	0%
Ikeoluwa, et al [23]	19.7%	4.7%
Keikhaei B, et al 2012 [24]	38.8%	2.9%
Lakhkar Bb, et al 2012 [25]	88%	8%

In this study SCD SS children had higher mean velocity than controls and the difference was statistically significant (p value is less than 0.05). Significant difference between SCD SS and control groups was also found by Valadi N et al, 2006, Margaret T. Lee, et al 2006, Prohovnik I, et al 2009, Keikhaei B, et al 2012[15,16,24].

In present study Females had higher Mean velocity in left ophthalmic artery as compared to males and the difference was significant statistically. (P value is less than 0.05) (Table 3).

Vavilala MS, et al 2005, Tontisirin N et al, 2007 found middle cerebral artery and basilar artery flow velocities to be higher in normal healthy girls than boys. Mohammad Ali Molavi et al 2012 found significant difference between male and female only in left common carotid artery and left Internal Cerebral Artery, and in both arteries, the systolic blood flow velocity was lower in female[17]. Margaret T. Lee, et al 2006 and M. Arkuszewski, et al 2011 didn't find significant difference in mean velocity between males and females[18].

The mean blood flow velocity among both genders was higher in SCD SS patients as compared to controls. (Table 3). The mean blood flow velocity of female with SCD SS was higher than female controls in following arteries right opthalmic artery, left MCA, left ACA, left ophthalmic artery and basilar artery.

Table 4 showed in the present study Mean velocity of intracranial arteries didn't show significant changes with age, where as in other study result were deferent i.e. blood flow velocity has had decrease by age increase in three groups of patients including fewer than seven, 7-10 and above seven. Although this decrement was not significant but it partially could justify the higher blood flow velocity in 2 -6 years group. The

findings of Henrietta et al 2004 & Adam et al. 2011 studies have shown that the maximum age of stroke prevalence is 4 years [18]. Children with SCA generally have high TCD velocities in all cerebral blood vessels compared to age-matched controls but there are few data available about velocities in infants with SCA less than 2 years of age.

Hogan et al. reported that infants with SCA had MCA velocities of 50 – 112 cm/sec (median 70) at 3 months of age, 50–160 cm/sec (median 89) at 9 months of age and 51–120 cm/sec (median 97) at 12 months of age. However, the sample size of this study was very small (n=14), TCD typically was recorded while the infant was sleeping, and there was no information provided about stroke

In the 1990s, Adams et al Demonstrated that an abnormal TCD is linked to high risk of a first stroke, and that chronic transfusions reduce this risk. One hundred ninety children were screened with TCD and followed for an average of 29 months; 23 had a TAMX >170 cm/s; strokes occurred in seven patients, including six among the 23 patients with abnormal TCD. This result was confirmed by a subsequent study including 125 more children, which showed that a TAMX≥200 cm/s in the terminal ICA, or in the MCA, indicates a 10% risk for stroke per year, compared to a 2% risk in patients with normal TCD[9,18].

The study, Stroke Prevention Trial in Sickle Cell Anemia (STOP), which included patients with SCA aged between two and 16 years, confirmed the predictive value of TCD for strokes in this patient population and demonstrated that blood transfusions considerably reduced the risk of strokes among children in this age range with abnormal TCD. additionally, these studies established their own parameters for the definition of abnormal TCD in this cohort of patients.

High velocities are related to stenosis as well as severe anemia and tissue hypoxia. Since the STOP trial, it has been recommended that children aged 2–16 years with SCD be screened by TCD to identify those at high risk for stroke. These high-risk children are then offered transfusion regimens for stroke prevention.

REFERENCE

1. M. Kamble and P. Chaturvedi. Epidemiology of sickle cell disease in a rural hospital of central India. Indian Pediatrics.2000; 37:391-396. | 2. R. S. Balgir. Spectrum of haemoglobinopathies in the state of Orissa, India. A ten years cohort study. J Assoc Physicians India.2005 Dec; 53:1021-1026. | 3. Lehmann H, Cutbush M, Sickle-cell trait in southern India. Br Med J. 1952 Feb 23; 1(4755):404-5. | 4. Negi RS., Sickle cell trait in India. A review of known distribution, Bull AnthropolSurv India. 1972; 17:439–449. | 5. Ambekar SS, Phadke MA, Mokashi GD, Bankar MP, Khedkar VA, Venkat V, Basutkar DG , Pattern of haemoglobinopathies in western Maharashtra. Indian Pediatr. 2001 May; 38(5):530-4. | 6. Pradeep K. Patra ,Virander S. Chauhan, Prafulla K. Khodiar, Abdul R. Dalla, and Graham R. Serjeant et al Screening for the sickle cell gene in Chhattisgarh state, India: an approach to a major public health problem J Community Genet. 2011 September; 2(3): 147–151 | 7. PROJECT IMPLEMENTATION PLAN 2012-13, CHHATTISGARH cg.nic.in/health/programonitoring/PIPHealthFinancing/PIP201213. | 8. Ohene-Frempong K, Weiner SJ, Sleeper LA, Miller ST, Embury S, Moohr JW, et al. Cerebrovascular accidents in sickle cell disease: rates and risk factors.Blood. 1998 Jan 1; 91(1):288-94. | 9. Robert Adams M.D. ,Virgil Mckie , M .D. et al the use of transcranial ultrasonography to predict stroke in sickle cell disease N Engl Med 1992;326:605-10. | 10. Adams RJ, McKie VC, Hsu L, et al. Prevention of a first stroke by transfusions in children with sickle cell anaemia and abnormal results on transcranial Doppler ultrasonography. N Engl J Med. 1998; 339(1):5-11. | 11. M. Schoning, MD; M. Staab, MD; J. Walter; G. Niemann, MD et al ,Transcranial Color Duplex Sonography in Childhood and Adolescence Age 136. Dependence of Flow Velocities and Waveform Parameters. Stroke. 1993; 24:1305-1309. | 12. Kimura K, Hashimoto Y, Hirano T, Uchino M, Ando M. et al, and Diagnosis of middle cerebral artery occlusion with transcranial color-coded real-time sonography AJNR Am J Neuroradiol. 1996 May; 17(5):895-9 . | 13. Adams RJ. Et al Lessons from the Stroke Prevention Trial in Sickle Cell Anaemia (STOP) study. J Child Neurol. 2000 May; 15(5):344-9. | 14. Bulas DI, Jones A, Seibert JJ, Driscoll C, O'Donnell R, Adams RJ et al ,Transcranial Doppler (TCD) screening for stroke prevention in sickle cell anaemia: pitfalls in technique variation. PediatrRadiol. 2000 Nov; 30(11):733-8. | 15. Margaret T. Lee, Sergio Piomelli, Suzanne Granger, Scott T. Miller, Shannon Harkness, Donald J. Brambilla, and Robert J. Adams et al Stroke Prevention Trial in Sickle Cell Anaemia (STOP): extended follow-up and final results ,Blood. 2006; 108:847-852. | 16. Valadi N, Silva GS, Bowman LS, Ramsingh D, Vicari P, Filho AC, Massaro AR, Kutlar A, Nichols FT, Adams RJ. et al Transcranial Doppler ultrasonography in adults with sickle cell disease. ,Neurology. 2006 Aug 22; 67(4):572-4. | 17. Mohammad Ali Molavi, MohammadRezaAlizade, Ahmad Negahi, YaghoobHamedi, AbdolmajidNazemi, KamyarMolavi et al Study of Transcranial Doppler in Children with Sickle-Cell Anaemia in Bandar Abbas Children's Hospital in Period of 2010- 2011 Asian Journal of Medical and Pharmaceutical Researches ,AJMPR Asian J. Med.Pharm.Res.2(1):16-20,2012.143. | 18. M.Arkuszewskia,b, J.Krejzaa,c,d, R.Chena, J.L.Kwiatkowskie, R.Ichordf,g, R. Zimmermanh, K. Ohene-Fremponge, L. Desiderioa and E.R. Melhema Sickle Cell 142 Disease: Reference Values and Interhemispheric Differences of Nonimaging Transcranial Doppler Blood Flow Parameters ,AJNR Am J Neuroradiol. 2011 Sep;32(8):1444-50. doi: 10.3174/ajnr.A2529. | 19. Adams R, McKie V, Nichols F, Carl E, Zhang DL, McKie K, Figueroa R, et al. The Use of Transcranial Ultrasonography to Predict Stroke in Sickle Cell Disease. N Engl J Med. 1992;326(9):605-10 125 . | 20. Pavlakis SG, Rees RC, Huang X, Brown RC, Casella JF, Iyer RV, Kalpatthi R, Luden J, Miller ST, Rogers ZR, Thornburg CD, Wang WC, Adams RJ; BABY HUG Investigators Transcranial doppler ultrasonography (TCD) in infants with 141sickle cell anaemia: baseline data from the BABY HUG trial.Pediatr Blood Cancer. 2010 Feb; 54(2):256-9. | 21. Clarisse Lopes de Castro Lobo, Rodolfo DelfiniCançado, Ana Claudia CelestinoBezerraLeite,Ana Claudia Mendonça dos Anjos et al Brazilian Guidelines for transcranial doppler in children and adolescents with sickle cell disease ,Rev Bras HematolHemoter. 2011; 33(1): 43–48. | 22. Mary Hokazono, Gisele Sampaio Silva, Edina Mariko Koga Silva, Josefina Aparecida Pellegrini Braga et al Results from transcranial | 23. Doppler examination on children and adolescents with sickle cell disease and correlation between the time-averaged maximum mean velocity and hematological characteristics: a cross-sectional analytical study Sao Paulo Med J. 2011; 129(3):134-8 | 24. IkeOluwaLagunjuOlugbemiroSodeinde and Paul Telfer et al Prevalence of transcranial Doppler abnormalities in Nigerian children with sickle cell disease ,American Journal of Haematology Volume 87, Issue 5, pages 544–547, May 2012 | 25. Keikhaei B, Mousakhani H, Oghbaee M et al Results of transcranial doppler in children with sickle cell disease: correlation between the time-averaged mean of maximum velocity and some hematological characteristics iranian journal of blood and cancer volume 5 number 1 autumn 2012 15 | 26. LakhkarBB ,Vaswani P , 2012, Transcranial Doppler Study Among Children with Sickle Cell Anaemia Vs Normal Children , J. Nepal Paediatr. Soc, May-August, 2012/ Vol 32/Issue 2. |