

To study the effect of hydroxyurea on transcranial doppler in patients with sickle cell anemia

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Background: The estimated rate of 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. The frequency of stroke in SCD is estimated at 0.61 per 100 patients per year. TCD is a valuable screening test in many clinical conditions such as SCD, to identify the patients at risk of stroke. An abnormally high blood speed is an indicator of a narrowed cerebral blood vessel and/or increased blood volume and a warning marker of high risk for stroke. **Methods:** This was a prospective comparative cross-sectional observational hospital based study, conducted over a period of 17 months (July 2016 to November 2017) in the Department Of Pediatrics and Radiodiagnosis, Dr. B.R.A.M.H, Raipur (C.G.). Children between 2 to 14 years diagnosed as SCD SS who were receiving long term (>6months) HU(hydroxyurea) treatment (cases) – HU group, and those who had never received this treatment (control) – HU naïve group, were enrolled. **Results:** The total number of children enrolled in the present study was 120, out of which 40 were cases and 80 were controls. The mean blood flow velocity of cases was significantly lower than controls. Among cases and controls maximum mean blood flow velocity was found in Left MCA followed by Right MCA. In addition to this, it was also found that there was no significant interhemispheric difference in both group. (p-value more than 0.05). **Conclusion:** The mean blood flow velocity in the HU group and HU naïve group was within the normal range (<170cm/sec), as per STOP criteria. The mean blood flow velocity in patients who were on the HU group was found to be significantly lower than the HU naïve group.

Keywords: Stroke in SSD, Transcranial doppler, Risk for stroke, HU-hydroxyurea

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Introduction

Sickle Cell disorders are a group of inherited genetic disorders and a major public health problem in Chhattisgarh. These disorders can be transmitted from one generation to the next through the Mendelian recessive type of inheritance. The public health implications of sickle cell disorders are significant. This impact on human health may be assessed against the yardsticks of infant mortality, under-five mortality, and maternal mortality. However, complete curative therapy for Sickle Cell Disorders is not available in any system of Medicine. Symptomatic and supportive treatment is the only mainstay [1-8].

Stroke is a serious complication of sickle cell disease. The majority of strokes are ischemic events caused by stenosis of large cerebral arteries. Stroke generally occurs without warning and cause significant long term neurologic sequelae in at least 50% of cases. Chronic transfusion therapy for children who suffer stroke decreases the recurrent stroke rate from 90 % to less than 10 % [1-8].

TCD is a valuable screening test in many clinical conditions such as SCD, to identify the patients at risk of stroke. An abnormally high blood speed is an indicator of a narrowed cerebral blood vessel and/or increased blood volume and a warning marker of high risk for stroke. Regular blood transfusion and treatment with Hydroxyurea can significantly reduce the incidence of stroke in children with SCD who are found to be at high risk of stroke based on abnormal TCD findings. Previous finding has demonstrated that routine TCD screening test in children with SCD can indicate the high risk group and is useful in recommending the initiation of regular blood transfusion or alternatively use of hydroxyurea. Our patients rarely complained of headache and limb weakness. This study was done out of curiosity to see whether our patients differed from patients elsewhere. The present study aimed, at measuring and comparing the TCD flow velocity in children of 2 years to 14 yrs with SCA SS with and without hydroxyurea [9-12].

Methods

A cross sectional study was performed at the Department of Pediatrics, Dr. B.R Ambedkar Hospital, Raipur, Chattisgarh, India between July 2016 and November 2017. The study protocol was approved by the Institutional Ethics Committee and Scientific Committee.

Inclusion criteria: Children between 2 to 14 years diagnosed as SCD SS who were receiving long term (>6 months) HU treatment (cases) – HU group, and those who had never received this treatment (control) – HU naïve group, were enrolled.

Exclusion criteria: Sickle cell patients who had received recent blood transfusions, had a painful crisis, fever, infections, h/o major head injury, h/o seizure disorder requiring anticonvulsant therapy, and who had h/o prenatal or perinatal hypoxicischemic brain injury were excluded.

All the transcranial Doppler examinations were performed in quiet and awake patients by the same professional who had been trained to perform transcranial Doppler using the machine Make and Model: -Toshiba, Model:

AplioMX, Model SSA-780A with a Toshiba Phased Array Transducer, (Model-PST 30BT 3 MHz), and following the criteria of the STOP (Stroke Prevention Trial in Sickle Cell Anaemia) study." From this examination, the time-averaged maximum mean velocities were determined every 2 mm along the following arteries: bilateral anterior cerebral, middle cerebral arteries, bilateral ophthalmic arteries and basilar artery using appropriate windows- trans temporal (MCA, ACA). Trans orbital (ophthalmic artery), sub occipital (basilar artery).

TCD was done in a total of 120 children with SCD, comprising of 40 in HU group and 80 in HU naïve group. It was done in the same condition of temperature and posture (supine) for both the groups. Before transcranial Doppler was done, enough time was given to them until their pulse rate and blood pressure would reach a stable condition. The surrounding environment was quietly calm and this provided the possibility of detecting low amplitude signals with high frequency.

TCD studies have been performed in steady state defined as crises free period extending from at least 3 weeks since last clinical event and 3 months or more since last blood transfusion, before the start of new clinical events. The highest value from the right or left middle cerebral arteries, anterior cerebral artery, ophthalmic arteries, and basilar artery was taken as the time averaged maximum mean velocity for each patient and was used in the data analysis. When the time-averaged maximum mean velocity result was conditional or abnormal, the examinations were repeated until two consecutive abnormal results were obtained.

As per STOP study velocities were classified as below [12, 13].

Normal < 170 cm/sec

Conditional - 170-199 cm/sec

High or abnormal > 200 cm/sec

Data was compiled in MS excel and checked for its completeness and correctness then it was analyzed by suitable statistical test (chi-square test and Test were applied) and P-value < 0.05 was conditional as statistically significant.

Results

The total number of children enrolled in the present study was 120, out of which 40 were cases and 80 were controls. Among 120 child patients, there were 83 male children and 37 female children i.e. 69.2% males and 30.8% females. Age variations in the series were from 2 years to 14 years, out of which the majority of the patient were in the age group of 6 to 10 years.

A majority of the subjects were vaccinated (94.2%). 92.5% among cases and 95% among controls were completely vaccinated with routine vaccines which were found to be non-significant. In this study Hemoglobin concentration of the majority of the subjects was 5-10gm. Maximum controls (80.0%) had hemoglobin concentration in 5-10 gm% range but with none had hemoglobin concentration in > 10gm% range. Hb status was significantly higher in cases than in the control group.

Also, it was found that, in the present study, the most common reason for the previous admission was a vaso-occlusive crisis (case 52.5% and controls 47.5%) followed by the hemolytic crisis (cases 27.5% and controls 35%) and blood transfusion (cases 12.5% and controls 11.2%).

In both cases and controls, the mean velocity was in the normal range (< 170 cm/sec) in all patients. Table 1 shows the distribution of the mean velocity of intracranial vessels in case and controls. The mean blood flow velocity of cases was significantly lower than controls (p<0.05). Among cases and controls maximum mean blood flow velocity was found in Left MCA followed by Right MCA. Table 2 shows the comparisons of mean velocities of intracranial vessels between cases and controls. In addition to this, it was also found that there was no significant interhemispheric difference in both group. (p-value more than 0.05).

There were no significant associations between blood flow of Right and Left Side of MCA, ACA and ophthalmic arteries among cases. Table 3 shows the interhemispheric difference in mean velocity in cases and controls.

Table 1. Distribution of mean velocity of intracranial vessels in case and controls.

	Cases n=40		Controls n= 80	
	Number	Percentage	Number	Percentage
Mean Velocity (Cm/Sec)				
Normal (<170)	40	100%	80	100%
Conditional(170-200)	0	0%	0	0%
High Risk (>200)	0	0%	0	0%

Table 2. Comparisons of mean velocities of intracranial vessels between cases and controls.

Case/Control		Right MCA	Right ACA	Right ophthalmic artery	Left MCA	Left ACA
Case	Mean	69.78375	61.2065	16.03625	74.93	60.7325
	Std. Deviation	16.99879	19.39805	4.13067	13.54076	15.28812
Control	Mean	86.5375	70.6045	37.94438	87.50875	73.57125
	Std. Deviation	24.35198	24.42169	20.69409	23.12311	19.59281
Total	Mean	80.95292	67.47183	30.64167	83.31583	69.29167
	Std. Deviation	23.47946	23.21754	19.93601	21.22501	19.19324

Table 3. The interhemispheric difference in mean velocity in cases and controls

	Case n = 40				Control n = 80			
	Right(Mean + Sem)	Left (Mean + Sem)	T test	P value	Right (Mean + Sem)	Left (Mean + Sem)	T test	P- value
MCA	69.7838.68775	74.9300+2.14098	1.498	.138	86.5375+2.72263	87.5087+2.58524	.259	.796
ACA	61.2065+3.06710	60.7325+2.41726	.121	.904	70.6045+2.73043	73.5712+2.19054	.848	.398
Ophth	16.0362+.65312	15.1912+.62619	.934	.353	37.9444+2.31367	38.4034+2.24560	.142	.887

Discussion

In this cross sectional hospital based study, the current observed that the Mean blood flow velocity of the HU group was lower than the HU naïve group. (P-value is less than 0.05), but none of the study subjects (SCA SS) had TCD flow velocity in conditional or high risk range as per STOP criteria. The finding of distribution of the mean velocity of intracranial vessels in the present study differed with the data from a similar study conducted by The Stroke Prevention Trial in Sickle Cell Anaemia (STOP) which reported prevalence of abnormal TCD in 6.72% of the studied patients (130/1934). Also, Robert Adams, et al 1992 found abnormal velocity (170cm/sec) in 23 out of 190 patients SCD SS (12%) [14]. Ariane S., et al, 2002 found the mean velocity in the MCA and ACA was 123.7 cm/sec and 99.43 cm/sec respectively [15]. Another observation made from this study was that the Mean blood flow velocity of the HU group was significantly lower than the HU naïve group. The maximum Mean blood flow velocity was found in Left MCA followed by Right MCA in both the groups. This was supported by the study of Zimmerman SA, et al which also indicated that hydroxyurea can significantly decrease elevated TCD flow velocities, often into the normal range [16]. They suggested a multicenter trial is warranted to determine the efficacy of hydroxyurea for the management of increased TCD values, and ultimately for primary stroke prevention in children with SCA.

In addition, it was also found that there was no significant interhemispheric difference in both groups. (p-value more than 0.05). No significant association was found between the blood flow of Rt. and Lt. Side of MCA, ACA and ophthalmic arteries among HU group and HU naïve group. This was in consonance with the data from the study conducted by Jesper Bay Hansen et al [17], Mikolaj A. Pawlak, et al [18], Mohammad Ali et al [19] which also showed no significant interhemispheric differences in mean velocity in both the groups.

Mohammad Ali Molavi, Mohammad Reza Aliz, Kamyar Molavi, et al conducted a study and found that in cases who have been treated with hydroxyurea blood flow velocity was less in comparison to those who did not take it which was same as other researches [19].

Melo, et al (In Sergipe), 2005 gathered data on 34 patients with sickle cell anemia, aged less than 18 years, and compared them with 80 controls.

Among the results from the patients, none of them (0,0%) presented abnormal time-averaged maximum mean velocity and four (11.7%) presented conditional results [18]. Park, et al (In São Paulo), 2006 evaluated 77 patients with sickle cell disease, aged between 2 and 16 years. They found two patients (2.6%) with abnormal time-averaged maximum mean velocity and li (14.3%) with conditional results [19]. Valadi N, et al, 2006 found adults with SCD had a higher mean time averaged maximum mean velocity (110.9±25.7cm/s) compared with healthy controls (71.1±12.0 cm/s), and the difference is approximately proportional to their anemia [20]. No cases with velocities ≥ 200 cm/sec were found in this sample.

Margaret T. Lee, et al found mean velocity (MV) of 125.69 cm/s, 123.40 and 79.44±15.54 in SCA patients (group1=34 patients) and Controls (group2=81 controls) respectively. MV differences were statistically significant between groups [21].

Conclusion

The current study concluded that the Mean blood flow velocity in the HU group and HU naïve group was within the normal range (<170cm/sec), as per STOP criteria. In the current study mean blood flow velocity in patients who were in the HU group was found to be significantly lower than the HU naïve group. However none of the patients under the study groups had TCD flow velocity in the high risk range as per stop criteria. Hence long term follow up studies are needed to conclusively assess the effect of hydroxyurea therapy on TCD flow velocity inpatient of SCA SS.

What does the study add to the existing knowledge?

Long term follow up studies are needed to conclusively assess the effect of hydroxyurea therapy on TCD flow velocity inpatient of SCA SS. The patients on hydroxyurea therapy had significantly lower TCD flow velocities as compared to those who did not.

Author's Contributions

Dr. Sharja Phuljhele, Dr. Prankur Pandey, Dr. Rajesh Banjare conceptualized, designed and analyzed the study, **Dr. Prankur Pandey** was directly involved in paper drafting,

Dr. Rajesh Banjare conducted the data collection and helped in analysis and manuscript writing.

Abbreviations : SCD: Sickle cell disease, SCA: Sickle cell anemia, HU: Hydroxyurea, MCA: Middle cerebral artery, ACA: Anterior cerebral artery, STOP: The Stroke Prevention Trial in Sickle cell anemia.

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