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

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Abstract

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 as 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 [1-8].

Methods: This was a prospective comparative cross-sectional observational hospital-based study, conducted over a period of 17 months (July-July 2016 to November-NOVEMBER 2017) in the Department Of Pediatrics and Radiodiagnosis, Dr R.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 presentour 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 groups. (p value more than 0.05).There was werenNo significant associations between blood flow of Right and Left Side of MCA, ACA and ophthalmic arteries among cases. Conclusion: The Mean 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, Ttranscranial Doppler, Rrisk for stroke, HU-hydroxyurea

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 systems of Medicine. Symptomatic and supportive treatment is the only mainstay.[1-8].

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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 high-risk group and is useful in recommending the initiation of regular blood transfusion or alternatively use of hydroxyurea. Our patients rarely complained of headaches 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 2years to 14yrs with SCA SS with and without hydroxyurea. [9-12].

Methods
A cross 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 14years diagnosed as SCD SS who were receiving long term (>6months) 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 hypoxic hypoxic-ischemic brain injury were excluded.

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

AploMX, 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 has have been performed in steady-state STEATY 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 –average-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 [12, 13] 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 t test was applied ) and P 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 was werefound to be non-significant. In this study Hemoglobin concentration of the majority of the subjects were was5-10gm. 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 vascular-occlusive crisis (case 52.5% and controls 47.5% ) followed by the hemolytic crisis (cases27.5% 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 groups. (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

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

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

| Case/Control | Right MCA | Right RIGHT ACA | Right 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       | 69.7838,6875  | 74.9300+2.1 | 1.498   | .138   | 86.5375+2.7 | 2263   | .259   | .796  |
| ACA       | 61.2065+3.06  | 60.7325+2.4 | .121   | .904  | 70.6045+2.7 | 3043   | .848  | .398  |
| Ophth     | 16.0362+,653  | 15.1912+,62  | .934   | .353  | 37.9444+,2.3 | 1367   | .142  | .887  |

**Discussion**

In this cross sectional cross-sectional hospital-based study, the current we 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 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 (170 cm/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.

MehmoodAliMolavi, MohammadRezaAliz, KamyrarMolavi, 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 anaemia, 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± +/- 25.7 cm/s) compared with healthy controls (71.1± +/- 12.0 cm/s), and the difference is approximately proportional to their anaemia [20]. No cases with velocities >/=200 cm/sec were found in this sample.

Margaret T. Lee, et al 2006 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.[2119].

Another observation made from this study was that Mean blood flow velocity of HU group was significantly lower than 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 (2007) [14] which also indicated that hydroxyurea can significantly decrease elevated TCD flow velocities, often into the normal range. 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. MohammadAliMolavi, MohammadRezaAliz, KamyrarMolavi, et al(2012) conducted a study and found that, in cases who has been treated with hydroxyurea blood flow velocity was less in compare to those who did not take it which was same as other researches.17

In addition , we also found that there was no significant inter hemispheric difference in both the groups. (p value more than 0.05). No significant association was found between blood flow of Rt. & Lt. Side of MCA, ACA & 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 1997, Mikolaj A. Pawlak, et al 2009, Mohammad Ali et al 2012 which also showed no significant interhemispheric differences in mean velocity in both the groups.

Conclusion

The current study concluded that We conclude that:
1. Mean blood flow velocity in the HU group and HU naïve group was within the normal range (<170 cm/sec), as per STOP criteria.
2. 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 high-risk range as per stop criteria.

Hence long term follow up studies are needed to conclusively access the effect of hydroxyurea therapy on TCD flow velocity inpatient of SCA SS.

What does this study adds to the existing knowledge?

Long term follow up studies are needed to conclusively access 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
analyzed the study, Dr. Prankur Pandey was directly involved in paper drafting and will be the primary correspondent author. 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 anaemia.

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**Ethical Approval:** This study was approved by the Institutional Ethics Committee

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