Original Article

A study about effect of hydroxyurea on scholastic performance of children with sickle cell anemia

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ABSTRACT

Background: Sickle cell anemia (SCA) is the most common hemoglobinopathy affecting the population worldwide, is associated with high morbidity and mortality. Treatment with hydroxyurea (HU) has shown promising results by improving the clinical profile of patients. However, its effect on scholastic performance of children is yet to be explored. **Objective:** The objective of the study was to evaluate the effect of HU on scholastic performance in children affected with SCA. **Methods:** A prospective analytical study was conducted among 73 SCA patients between the ages of 5 and 14 years hospitalized or visiting the outpatient department at a tertiary care center on Central India. A fixed low dose of HU (20 mg/kg/day) was prescribed to individual patients at the start of the study. Patients were followed up for a period of 6 months at an interval of 2 months. Scholastic performance was evaluated based on school attendance and examination grades of child and was compared with results of previous year. **Results:** Only 54/73 patients successfully completed the study, among them 51.8% were male. Vaso-occlusive crisis (VOC) was the most common indication for initiating HU therapy. After 6 months of active therapy, significant improvement in scholastic performance was observed. Improvement in mean attendance from 63.98% to 68.09% was observed ($p<0.05$). Similarly, improvement in study grades was observed in 33.3% ($p=0.001$). No adverse reaction due to HU was noticed during study period. **Conclusion:** HU is a safe and an effective drug which can be used to prevent VOC in SCA patients. Apart from this, it also improves the scholastic performance in these children.

Keywords: Hemoglobin S, Hydroxyurea, Scholastic performance, Sickle cell anemia, Vaso-occlusive crisis

Sickle cell disease is an autosomal recessive hemoglobinopathy and is the common cause of hemolytic anemia in children resulting in decreased life expectancy by 15–30 years. In sickle cell anemia (SCA), both β-globin chains are affected due to homozygous gene mutation. While, sickle cell disease is a combination of hemoglobinopathies including SCA, hemoglobin (Hb) C, Hb S ß-thalassemia, Hb D, and Hb O due to heterozygous gene defects β-globin chains. During hypoxic conditions, the qualitative defect present in the β-chain of Hb beta-chain causes an alteration in the shape of red blood cells known as sickling. These sickle cells fail to cross the capillary endothelium subsequently resulting in various complications which require hospitalizations. Clinical presentation and disease severity is directly correlated to the percentage of Hb S in total Hb. While, in patients with SCA, Hb S accounts for 90% of the total Hb, Hb S is >50% of total Hb in sickle cell disease [1].

Among the various clinical manifestations of SCA, vaso-occlusive crisis (VOC), aplastic crisis, dactylitis, acute chest syndrome, splenic sequestration, priapism, and stroke are reported in patients with severe SCA. In addition, SCA is known to affect the scholastic performance of children [2-4]. It is believe that silent stroke associated with SCA is one of the common reasons for poor cognitive functions that affect the school performance [5,6]. Since, scholastic performance is one of the important milestones in a child; its impairment has long-lasting effect on child's mental status and future life. Sickle cell disease in itself or in combinations with its various complications, recurrent hospitalization has an impact on psychological effect on child resulting poor scholastic performance [7,8]. Since no definite treatment is available to correct the underlying genetic defect, management of SCA comprises symptomatic and supportive treatment. Among these, hydroxyurea (HU) is the only disease modifying drug available for treatment in SCA. It boosts the formation of Hb F which has high affinity for oxygen, thereby decreasing the Hb S% in RBCs, chances of sickling and its associated complications [9].

SCA is an endemic disease of Central India with increased frequency of patients having painful episodes necessitating hospitalization. Although, HU is beneficial in prevention of

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these episodes, since the drug is prescribed for a long duration, it is very important to analyze its effect on whole body including growth, development, systems, and scholastic performance. Various studies in the past found it a safe and effective drug. HU is believed to have a beneficial effect on different systems of the body and its role has been widely studied [10-12]. Education is a very crucial part of child's development and future life. However, studies related to the role of HU on child's scholastic performance are limited. Hence, the present study was planned to evaluate effect of HU therapy on scholastic performance of children with SCA.

MATERIALS AND METHODS

A prospective analytic study was conducted to assess the effect of HU on scholastic performance in 74 children with SCA in a tertiary care center of Central India from August 2014 to September 2015. School-going children diagnosed with SCA between the age of 5 and 14 years either attending outpatient department or hospitalized due to various complains of SCA were included in the study. Patients diagnosed with sickle cell trait, other hemoglobinopathies, and those already on HU were excluded from the study. Need of study was explained to the parents or guardians and an informed consent was obtained before the study. All relevant demographic, clinical and laboratory parameters, and scholastic details filled in a predesigned pro forma specific for the study.

A fixed low-dose HU (20 mg/kg/day) was started as per recommendation in all enrolled patients. They were followed up and monitored at 2-month intervals for a period of 6 months. Scholastic performance was evaluated based on two parameters, that is, school attendance and performance in examinations (grades). These two parameters were compared with last year attendance and grades in examinations when the patient was not on HU therapy. Patients who were lost to follow up, poor compliance, death, or any major adverse reaction required discontinuation of HU therapy and those not providing relevant clinical or scholastic details were not included in the final analysis.

Obtained qualitative and quantitative data were subjected to statistical analysis using SPSS 16 trial. Mean, ratio, and rate were calculated. Paired t-test and Fisher's exact test were used to compare the effect of HU therapy in children with SCA. $p<0.05$ was considered statistically significant.

RESULTS

Among 73 patients enrolled for the study, 19 patients did not complete the study due to the various reasons mentioned above. Therefore, only 54 patients who successfully completed follow-up were included for final analysis (Fig. 1). In the study cohort, 51.8% were boys and 48.1% were girls, male:female ratio (M:F ratio) was 1.07: 1. The most common clinical presentation in SCA patients was recurrent VOC with a frequency of ≥3 episodes per year (29, 53.7%), followed by VOC with frequent blood transfusions (14, 25.9%) and frequent hospital admission (5, 9.2%), stroke (1, 1.8%), and others (5, 9.2%). During 6-month follow-up, a marked improvement in the school attendance of children with SCA was observed. Mean attendance before HU therapy was 63.98% which increased to 68.09% after 6 months of HU therapy but the difference was not significant (p=0.68).

HU therapy resulted in improvements in children's performance and no deterioration of grades and school attendance was reported in any child during the study period. Overall improvement in grades was observed in 33.3% of patients. Before starting therapy, 12 (22.2%) and 14 (25.95%) students had higher grades (A and B, respectively) which were improved to 20 (37%) and 16 (29.6%) students after 6 months of therapy. Similarly, Grades C and D were observed in 23 (42.6%) and 5 (9.2%) patients, respectively, which decreased to 15 (27.8%) and 3 (5.6%), respectively, after 6 months of HU therapy. Grades A and B were categorized as high grades while Grades C and D were categorized as low grades. Comparisons of mean attendance percentage and school grades are summarized in Table 1 which show a significant improvement in school performance (p=0.001). No significant adverse reaction and death were reported during the study period. Drug compliance was good as reported by children and parents. Furthermore, no significant life event which could affect school performance during this period was reported including change in socioeconomic condition, family or school atmosphere, or any other stressful condition.

DISCUSSION

A total of 54 children completed the study and the study group was almost equal in sex distribution and boys marginally outnumbered the girls. Most common cause for hospital visit was painful crisis. The previous studies have reported the academic performance of SCA children by comparing the IQ and cognitive functions between children with SCA and normal unaffected children. They observed a significant difference in IQ level and neuropsychological domain between both groups [8,12,13]. Other researchers have studied the effect on specific domain and inferred that SCA affects language, visual, motor, and memory, while another study reported that poor school performance associated with concentration and attention abilities of children [3-5]. In addition, SCA affects various domain of scholastic performance including academic achievements, cognitive ability, and grades in school. Al-Saqladi [8] reported scholastic difficulties in 80% of children while Crosby *et al*. [14] reported difficulty in scholastic performance in 60% of children.

Table 1: Comparison of the effect of HU therapy on scholastic performance of children

Parameters of scholastic performance	Before starting HU therapy	6 months after HU therapy	p-value
Mean school attendance	63.98%	68.09%	0.68
Grade, n (%)			
High (A and B)	26 (48.1%)	36 (66.7%)	0.001
Low (C and D)	28 (51.9%)	18 (33.3%)	

HU: Hydroxyurea

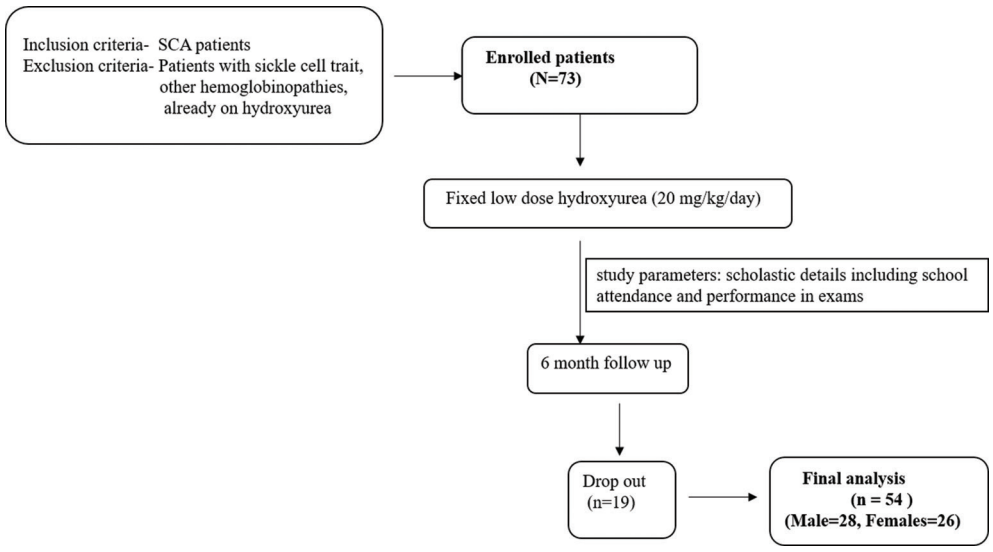

Figure 1: Flowchart depicting the study design

Effect of HU therapy on scholastic performance among SCA patients is yet to be explored. HU therapy decreases frequency of recurrent hypoxia, anemia and silent or overt stroke, acute episodic painful crisis, and repeated hospitalization thereby reducing the number of sick days. This ultimately improves the scholastic performance, achievements, and overall well-being of the patient. Similarly, we observed significant improvement in scholastic performance in patients with SCA after HU therapy. Improvement was directly proportional to the duration of HU therapy. Patients on more than 6 months of HU therapy had higher school attendance than before starting therapy.

According to Schatz [15], school outcome is best determined by combined scholastic achievement and attainment. They observed that attainment is problems are more prevalent in patients with sickle cell disease (31%) in comparison to control group (14%). Similarly, general cognitive ability was lower in SCA children as compared to the control group. Results of our study are comparable to the results of Schatz [15], wherein number of students achieving higher grades improved in both studies. Thaniel [16] studied cognitive development between siblings of SCA and suggested that there is scope of improvement in the cognitive performance. Schwartz *et al*. [5] in their study inferred that despite having clear academic goals, school absenteeism is a big problem among teenagers. However, when absenteeism was correlated with health-related and psychosocial variables, no significant association was noted. In the present study, 33.3% of students reported upgradation of their grades.

Silent stroke is a serious threat for normal brain functioning with an increased risk of recurrence. It is one of the major causes for poor school performance. Thornburg *et al*. [17] reported that on in patients taking HU, magnetic resonance imaging brain showed no recurrence of stroke and a decrease in transcranial Doppler velocity was also observed. This suggests that HU decreases the chance of stroke, especially silent stroke in SCA patients. Similar results are documented in the literature [18,19]. Similar to a study by Jain *et al*. [20], patients in our study required less blood transfusion and there was decreased fervency of hospitalization, moreover, no adverse reaction reported during the study period. Small sample size and short study duration are few of the limitations of our study. A longitudinal study with a longer follow-up longer carried out in a larger sample size is suggested to validate the results of the present study.

CONCLUSION

HU is safe drug that can be effectively in patient with SCA. On prolonged use, it not only improves the patient's underlying disease condition including painful crisis but also improves their scholastic performance.

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