DOI: 10.7860/JCDR/2022/57120.16922

Original Article

Paediatrics Section

Effect of Counselling on Compliance of Hydroxyurea Therapy and Frequency of Hospital Admissions among Patients with Sickle Cell Disease- A Longitudinal Study

GAURAV KUMAR PRAJAPATI[1], SHWETA SHARMA[2], JYOTSNA SHRIVASTAVA[3]

ABSTRACT

Introduction: Sickle Cell Disease (SCD) is an autosomal recessive multisystem disorder, characterised by anaemia, recurrent episodes of pain and chronic organ damage. Hydroxyurea (HU), a disease modifying agent with proven efficacy in reducing painful episodes in SCD patients thereby improving quality of life. Compliance to hydroxyurea therapy is a liming factor in management of SCD.

Aim: To compare adherence to HU therapy and frequency of hospital admissions before and after counselling.

Materials and Methods: This longitudinal study was conducted in Department of Paediatrics at Gandhi Medical College and associated Hamidia Hospital Bhopal, Madhya Pradesh, India, from 1st January 2020 to 30th June 2021. Patients with SCD, between the age group of 1-14 years, during study period were recruited. After enrollment, data regarding HU therapy and admissions in the previous one year was recorded for each registered patient. This was followed by detailed counselling sessions, which were repeated after three monthly intervals for a period of one year. Postcounselling data collection was done to evaluate the response. The effect of counselling was assessed using Chi-square test (for categorical variables) and Analysis of Variance (ANOVA) or paired t-test (for continuous variables). A p-value <0.05 was considered statistically significant.

Results: Initially, a total of 42 patients were registered, out of which only 31 patients could be followed-up till the last counselling. Mean age of the patients was 7.8±3.5 years, and 20 (64.5%) cases were males. As per history and previous year data total of 26 (83%) patients were already on HU therapy. Frequency of crises, hospital admissions, school absenteeism, and blood transfusion reduced significantly post counselling. The common factor associated with non adherence to therapy were non availability of drugs 21 (67.7%), followed by improper follow-up 20 (64.5%) and unawareness 17 (54.8%). Financial problems, non-palatability and distance from the hospital were other associated factors in 11 (35.5%), 4 (12.9%) and 2 (6.5%) cases, respectively.

Conclusion: With counselling, better drug compliance to HU therapy was observed. This is expected to help in achieving better disease control in terms of reduced need for blood transfusion, hospital admissions as well as school absenteeism.

Keywords: Absenteeism, Anaemia, Compliance

INTRODUCTION

Sickle Cell Disease (SCD) is a genetically inherited autosomal recessive disease [1]. It is monogenic multisystem disorder, which is characterised by anaemia, recurrent episodes of pain, chronic organ damage leading to infarction. This disease significantly affect the quality of life and is associated with reduced life expectancy [2,3]. The term SCD encompasses a group of hemoglobinopathies resulting from structural change in haemoglobin due to substitution of valine for glutamic acid at sixth position of β subunit [4], which leads to formation of abnormal haemoglobin called HbS [1,5]. Sickle cells loses the flexibility of normal haemoglobin, leading to formation of sticky membrane that is adherent to small capillaries and venules. All these alterations lead to recurrent episodes of micro vascular occlusion (infarction) that are responsible for characteristic clinical features associated with the condition. These features include recurrent pain crisis, acute haemolytic crisis, tissue ischaemia and end organ damage [6,7].

Hydroxyurea (HU), a disease-modifying agent is a very effective drug with proven efficacy in reducing painful episodes associated with sickle cell disease [8]. It is an antimetabolic, cytotoxic and antineoplastic agent with myelosuppressive properties. Hydroxyurea (HU) acts as a potent inhibitor of Ribonucleotide Reductase (RR) which is involved in DNA synthesis and repair. However, when the effect of hydroxyurea is removed this enzyme spontaneously regenerates into its active form. Thus, hydroxyurea when given once a day leads to intermittent cytotoxic suppression of progenitor of erythroid series, which in turn affects the physiology of erythropoiesis with increase HbF (foetal haemoglobin) levels [8].

As SCD requires lifelong therapy, adherence to drug regimen is important factor in determining recurrence of symptoms, development of complications, frequency of hospitalisation and the quality of life of affected individual. There are challenges to the HU therapy such as heterogeneity of the disease and response, timely and optimal prediction of dose, non adherence to treatments, incomplete understanding of the drug mechanism and myelosuppression [9].

This study aimed to compare adherence to hydroxyurea therapy, frequency of hospital admissions before and after counselling and to know the reasons for non adherence to HU therapy among SCD patients.

MATERIALS AND METHODS

This longitudinal study was conducted in Department of Paediatrics at Gandhi Medical College and associated Hamidia Hospital Bhopal, Madhya Pradesh, India, from 1st January 2020 to 30th June 2021. The study received ethical clearance from Institutional Ethics Committee, (letter number: 528/MC/IEC/2020; dated 4/01/2020).

All the patients of SCD registered in the Department of Paediatrics Gandhi Medical College, Bhopal were registered for the study. Out of total 42 patients (institutional incidence), for 31 patients the data

was analysed (five were started on the therapy at the time of study, and six could not be followed-up).

Inclusion criteria: All the patients of SCD, registered with the Department of Paediatrics, aged between 1-14 years, whose parents gave written consent were included in the study.

Exclusion criteria: Patients with other haemolytic disorders (sickle thalassaemia/thalassaemia) and for which hydroxyurea therapy started at registration by us were excluded from the study.

Detailed history regarding age at diagnosis, history of consanguineous marriage, family history regarding presence of similar disease in related sibling were taken. All the patients were subjected to detailed physical examination and anthropometric evaluation. Vitals such as pulse, blood pressure, respiratory rate were recorded. Nutrition in patients was defined according to World Health Organisation (WHO) definition of severe acute malnutrition [10].

Study Procedure

Data related to HU and folic acid therapy in terms of dose/kg, approximate number of missed doses per month in the last one year were noted. History was obtained regarding pattern of crisis, frequency of crisis, mean number of days of school absenteeism per month, number of hospitalisations and frequency of blood transfusion during previous one year.

Counselling: The Counselling was given to the parents and patients regarding disease and its management options, types of crises and management. Relevant information for drug therapy including mechanism of action, benefits and associated adverse effects was communicated. Parents were informed about investigations required during drug therapy, effect on disease after withdrawal/discontinuation of drug therapy and need for regular follow-up. Counselling was done in four sessions by two investigators, first at the time of registration then subsequently at three, six and nine months or at after three months. Information regarding drug intake, admission and blood transfusion during the ongoing year were again obtained and finally results were analysed at the end of 12 months of study. Both the data were compared and analysed.

STATISTICAL ANALYSIS

Data was compiled using Microsoft Excel and analysed using Statistical Package for Social Sciences (IBM SPSS software) version 20.0. Categorical variables were expressed as frequency and percentage whereas continuous variables were expressed as mean and standard deviation. The effect of counselling was assessed using chi square test (for categorical variables) and Analysis of Variance (ANOVA) or paired t test (for continuous variables). A p-value less than 0.05 was considered statistically significant.

RESULTS

The study included 31 patients of SCD. As per history and previous year data total of 26 (83%) patients were already on HU therapy. Mean age of the patients was 7.8±3.5 years [Table/Fig-1]. According to the modified Kuppuswami scale [11], majority (43%) were from the middle/lower middle class of socio-economic status. History of consanguineous marriage was there in 6.5% cases, whereas in 29% cases sibling was also found to be affected with SCD. Approximately half of the patients had malnutrition according to WHO criteria. In under five-year age, moderate malnutrition was the most common form observed in 32.3% cases while 11.1% cases had severe malnutrition. A 16.1% cases above the age of five year had under nutrition.

The most common factor associated with non adherence to HU therapy was unavailability of drugs (67.7%), followed by infrequent follow-up 20 (64.5%) [Table/Fig-2].

Variables	Values
Age (years)	
≤5	9
6-10	12
>10	10
Mean age (Mean±SD)	7.8±3.5 years
Gender (N, %)	
Male	20 (64.5%)
Female	11 (35.5%)
Residence	
Urban	21 (67.7%)
Rural	10 (32.3%)
Socio-economic status	
Upper middle	7 (22.6%)
Middle/lower middle class	13 (42%)
Lower/upper lower	11 (35.4%)
Consanguinous marriage	
Yes	2 (6.5%)
No	29 (93.5%)
Sibling with SCD	
Yes	9 (29.9%)
No	22 (70.1%)
Malnutrition	
Moderate malnutrition	3 of 9 (33.3%)
Severe malnutrition	1of 9 (11.1%)
Under nutrition (>5 years age only)	4 of 22 (18.1%)

[Table/Fig-1]: Demographic data.

Factors for non adherence	Frequency (n=31)
Non availability of drug	21 (67.7%)
Infrequent follow-up	20 (64.5%)
Unawareness	17 (54.8%)
Financial problem	11 (35.5%)
Non palatability	4 (12.9%)
Distance from hospital	2 (6.5%)

[Table/Fig-2]: Distribution of factors for non adherence to hydroxyurea.

Mean dose received daily by each patient was 22 mg/kg. Mean days of missed HU doses per month was 3.61±1.407 days (95% CI 3.10-4.13) in the previous one year, which reduced significantly at final follow-up to 1.42±0.672 (p-value=0.001). Folic acid was given along with HU therapy. Repeated counselling was significantly associated with reduction in missed mean folic acid dose in patients as compared to the previous one year, from 3.25 to 1.55. Counselling regarding importance of HU therapy was associated with significant reduction in school absenteeism, reflecting that the disease was in stable phase. The school absenteeism days reduced significantly from 5.13±1.979 days per month during the previous one year to 1.90±1.221 at final follow-up (p-value=0.001) [Table/Fig-3-5].

Mean number of HU dose missed per month	Mean	95% CI
In previous one year	3.61±1.407	3.10-4.13
3 months	1.29±0.902	0.96-1.62
6 months	1.61±0.919	1.28-1.95
9 months	1.39±0.615	1.16-1.61
At 12 months follow-up	1.42±0.672	1.17-1.67
ANOVA	33.6	
p-value	0.001	

[Table/Fig-3]: Effect of counselling on compliance of hydroxyurea therapy.

Sessions of counselling	Mean FA Dose missed per month (Days per month)	95% CI
Baseline (One year)	3.35±1.603	2.77-3.94
12 months	1.55±0.850	1.24-1.86
T-test	5.53	
p-value	0.001	

[Table/Fig-4]: Effect of counselling on compliance of folic acid therapy.

Parameters	Mean	95% CI	p-value (T test)
Hospital admission			
Baseline (previous one year)	2.03±0.912	1.70-2.37	0.001
12 months	0.81±0.654	0.57-1.05	
School absenteeism			
Baseline (previous one year)	5.13±1.979	4.40-5.85	0.001
12 months	1.90±1.221	1.46-2.35	
Requirement of blood transfusion			
Baseline (previous one year)	1.58±0.886	1.26-191	0.001
12 months	0.71±0.693	0.46-2.35	

[Table/Fig-5]: Effect of counselling on Hospital admission rate.

DISCUSSION

In SCD, lifelong hydroxyurea therapy is recommended, which is an effective drug with proven efficacy for management of these patients [8]. Adherence to drug is an important factor which may be a determinant of quality of life, recurrence of symptoms as well as need for transfusion and hospitalisation [12].

Counselling is one of the key factors which may help in eliminating various barriers associated with low adherence to HU therapy [13]. The study aimed at emphasising the effect of counselling on adherence to HU therapy and disease course. Mean number of HU dose missed per month during previous one year was 3.61±1.407 (95% CI: 3.10-4.13), whereas that after repeated counselling reduced significantly to 1.42±0.672.

Due to the Coronavirus Disease 2019 (COVID-19) pandemic some of counselling sessions were done telephonically. Creary S et al., used different approach (Mobile DOT) to improve the adherence to SCD as compared to present study, but the outcome was same i.e. increased compliance to hydroxyurea and decreased hospitalisations rates with improved clinical outcomes [13]. Halaharvi H et al., also highlighted the importance of counselling in improving the adherence to HU therapy by educating the patients or guardian regarding mechanism of action, benefits as well as risks of hydroxyurea therapy which in turn may have positive effect on overall outcome in such cases [14]. The present study findings were also supported by Ofkunrin AO et al., where HU was initiated in SCD patients and adherence to this drug was assessed by counselling especially of parents or older study participants, and HU therapy was significantly associated with better outcomes in such children due to better compliance to HU therapy [15].

Since, counselling improved the compliance to HU therapy as well as folic acid therapy, need for blood transfusion and school absenteeism rates reduced significantly, reflecting better control of the disease. Nnebe-Agumadu U et al., also found with use of hydroxyurea therapy in SCD patients' improvement in general condition was 91.25%, reduction in bone pain 83.3%, hospital admissions 71.9%, abdominal pain 62.3%, and blood transfusion 56.1% [16].

Various factors may affect the adherence especially in low- income and middle-income countries like India which include availability of drug, socio-economic status, health seeking behaviour and affordability [17,18].

The common factors associated with non adherence to hydroxyurea in decreasing frequency were non availability of drug, improper follow-up, unawareness, non affordability, non palatability and distance from hospital. In the present study, no side-effects of drug have been observed. However, Cabana MD et al., documented adherence to hydroxyurea in only 46% for SCD and low adherence was associated with a lack of outcome expectancy improved after proper counselling [19]. Thornburg CD et al., reported non adherence in six out of 75 children which was due to its long-term requirement, associated splenomegaly and myelosuppression, affordability and lack of transport means [20].

Brandow AM and Panepinto JA, documented the provider related, patient related and system related barriers to the effectiveness of hydroxyurea. Provider related includes compliance to the use of drug and side effects associated with drug. Patient related barriers include lack of compliance, refusal to take drug due to fear of complications, cost as well as availability of drug. However, system related barriers may be due to disproportionate demographic distribution of patients with sickle cell disease. Other systems-level barriers affecting compliance are composed of the lack of a medical home, limited access to specialised sickle cell centers, lack of care co-ordination between comprehensive sickle cell centers and community-based physicians for those beneficiaries that are geographically isolated from a comprehensive sickle cell center, and poor transition from pediatric to adult care [21]. In the present study infrequent follow-up, non availability of drugs, unawareness, financial problems, non palatability, distance from hospital were the factors for non adherence to the therapy.

Limitation(s)

Effect of HU therapy was studied in terms of only the clinical profile of patients and not based on laboratory parameters and biochemical profile. Effect of lockdowns on the study results due to the pandemic could not be ruled out.

CONCLUSION(S)

Sickle cell disease, being a chronic disorder, requires lifelong hydroxyurea therapy to control the disease and reduce the complications and suffering of children. However, adherence to hydroxyurea therapy is one of the major concerns which may be affected by multiple factors, most common being their non availability. Counselling of parents or older children can help in achieving not only disease control but also improving overall quality of life in terms of reduced need for blood transfusion, hospitalisation as well as school absenteeism.

REFERENCES

[1] Mangla A, Ehsan M, Agarwal N, Maruvada S. Sickle Cell Anemia. In: StatPearls. Treasure Island (FL): StatPearls Publishing; 2021 Jan. Available from: https://www.ncbi.nlm.nih.gov/books/NBK482164/.
[2] Chakravorty S, Williams TN. Sickle cell disease: A neglected chronic disease of increasing global health importance. Arch Dis Child. 2015;100(1):48-53.
[3] Sedrak A, Kondamudi NP. Sickle Cell Disease. In: StatPearls. Treasure Island (FL): StatPearls Publishing; 2021 Jan. Available from: https://www.ncbi.nlm.nih.gov/books/NBK482384/.
[4] Murayama M. Structure of sickle cell hemoglobin and molecular mechanism of the sickling phenomenon. Clinical chemistry. 1967;13(7):578-88.
[5] Rao VR. Genetics and epidemiology of sickle cell anemia in India. Indian J Med Sci. 1988;42:218-22.
[6] Leikin SL, Gallagher D, Kinney TR, Sloane D, Klug P, Rida W, et al. Mortality in children and adolescents with sickle cell disease. Pediatrics. 1989;84(3):500-08.
[7] Prasad R, Hasan S, Castro, Perlin E, Kim K. Longterm outcomes in patients with sickle cell disease and frequent vaso-occlusive crises. Am J Med Sci. 2003;325(3):107-09.
[8] Agrawal RK, Patel RK, Shah V, Nainiwal L, Trivedi B. Hydroxyurea in sickle cell disease: Drug review. Indian J Hematol Blood Transfus. 2014;30(2):91-96.
[9] Pandey A, Estepp JH, Ramkrishna D. Hydroxyurea treatment of sickle cell disease: Towards a personalized model-based approach. J Transl Genet Genom. 2021;5:22-36. http://dx.doi.org/10.20517/jtgg.2020.45.
[10] https://en.wikipedia.org/w/index.php?title=Malnutrition&oldid=1095718555.
[11] Anjali M, Khapre M, Asha TJ, Rahul A. Modified Kuppuswamy socio-economic status scale with 2016 as base year- An update for 2021. J Med Evid. 2021;2:234-35.
[12] Brawley OW, Cornelius LJ, Edwards LR, Gamble VN, Green BL, Inturrisi C, et al. National Institutes of Health Consensus Development Conference statement: Hydroxyurea treatment for sickle cell disease. Ann Intern Med. 2008;148(12):932-38.

[13] Creary S, Chisolm D, Stanek J, Hankins J, O'Brien SH. A multidimensional electronic hydroxyurea adherence intervention for children with sickle cell disease: Single-arm before-after study. JMIR mHealth and uHealth. 2019;7(8):e13452
[14] Halaharvi H. Barriers that prevent initial prescription of hydroxyurea in sickle cell disease. Theses and Graduate Projects. 2019;955.
[15] Ofakunrin AO, Oguche S, Adekola K, Okpe ES, Afolaranmi TO, Diaku-Akinwumi IN, et al. Effectiveness and safety of hydroxyurea in the treatment of sickle cell anaemia children in Jos, North Central Nigeria. J Trop Pediatr. 2020;66(3):290-98.
[16] Nnebe-Agumadu U, Adebayo I, Erigbuem I, James E, Kumode E, Nnodu O, et al. Hydroxyurea in children with sickle cell disease in a resource-poor setting: Monitoring and effects of therapy. A practical perspective. Pediatr Blood Cancer. 2021;68(6):e28969.
[17] Zimmerman SA, Schultz WH, Davis JS, Pickens CV, Mortier NA, Howard TA, et al. Sustained long-term hematologic efficacy of hydroxyurea at maximum tolerated dose in children with sickle cell disease. Blood. 2004;103(6):2039-45.
[18] Olivieri NF, Vichinsky EP. Hydroxyurea in children with sickle cell disease: Impact on splenic function and compliance with therapy. J Pediatr Hematol Oncol. 1998;20:26-31.
[19] Cabana MD, Kanter J, Marsh AM, Treadwell MJ, Rowland M, Stemmler P, et al. Barriers to pediatric sickle cell disease guideline recommendations. Global Pediatric Health. 2019;6:2333794X19847026.
[20] Thornburg CD, Calatroni A, Telen M, Kemper AR. Adherence to hydroxyurea therapy in children with sickle cell anemia. J Pediatr. 2010;156(3):415-19.
[21] Brandow AM, Panepinto JA. Hydroxyurea use in sickle cell disease: The battle with low prescription rates, poor patient compliance and fears of toxicities. Expert Rev Hematol. 2010;3(3):255-60.

PARTICULARS OF CONTRIBUTORS:
1. Postgraduate Student, Department of Paediatrics, Gandhi Medical College, Bhopal, Madhya Pradesh, India.
2. Associate Professor, Department of Paediatrics, Gandhi Medical College, Bhopal, Madhya Pradesh, India.
3. Professor and Head, Department of Paediatrics, Gandhi Medical College, Bhopal, Madhya Pradesh, India.

NAME, ADDRESS, E-MAIL ID OF THE CORRESPONDING AUTHOR:
Dr. Shweta Sharma,
Associate Professor, Department of Paediatrics, Hamidia Hospital,
Bhopal, Madhya Pradesh, India.
E-mail: sharmadrshweta77@gmail.com

PLAGIARISM CHECKING METHODS: [Jain H et al.]
- Plagiarism X-checker: May 02, 2022
- Manual Googling: Jul 04, 2022
- iThenticate Software: Aug 30, 2022 (9%)

ETYMOLOGY: Author Origin

AUTHOR DECLARATION:
- Financial or Other Competing Interests: None
- Was Ethics Committee Approval obtained for this study? Yes
- Was informed consent obtained from the subjects involved in the study? Yes
- For any images presented appropriate consent has been obtained from the subjects. NA

Date of Submission: **Apr 16, 2022**
Date of Peer Review: **May 18, 2022**
Date of Acceptance: **Jul 08, 2022**
Date of Publishing: **Sep 01, 2022**