ORIGINAL RESEARCH

An evaluation of effect of Hydroxyurea on frequency of blood transfusion, vasoocclusive crisis and hospitalisation in children of sickle cell disease

[1]Devraj Singh, [2]Prachi Choudhary, [3]Shikha Gupta, [4]Preeti Malpani

[1]Senior Resident, Department of Pediatrics, Gajra Raja Medical College, Gwalior, Madhya Pradesh, India
[2]Associate Professor, Department of Pediatrics, MGM Medical College, Indore, Madhya Pradesh, India
[3]Senior Resident, Department of Pediatrics,Government Medical College, Datia, Madhya Pradesh, India
[4]HOD, Department of Pediatrics,MGM Medical College, Indore, Madhya Pradesh, India

Corresponding Author
Shikha Gupta
Senior Resident, Department of Pediatrics, Government Medical College, Datia, Madhya Pradesh, India
Email: shikhagupta796@gmail.com

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ABSTRACT
Background: Hydroxyurea therapy is a known effective and safe therapy for the treatment of sickle cell anemia (SCA). Although it is used worldwide in our Indian based setup, it is underutilized not only due to economic reasons but also due to unaware practitioners about its use. **Methods:** An ambispective observational study was performed at our tertiary care center over a period of 1 year 8 months. One hundred and ninety patients were enrolled after taking a complete history, then started on Hydroxyurea and followed up every 2 months till 1 year. On follow-up, frequency ofvaso-occlucive crisis, blood transfusion andhospitalization was noted along with routine investigations and for any side effects. **Results:** Of 190 total recruited patients, 84 were studied at the end because of loss to follow-up due to various reasons. Significant decrease in the frequency of vaso-occlusive crisis, blood transfusion and hospitalisationwas observed within 1 year of starting Hydroxyurea (p<0.05). **Conclusions:** The use of hydroxyurea in our native population at our setup can decrease the frequency of vasooccluisve crisis, blood transfusion and hospitalisation in sickle cell patients.
Key words: Sickle cell anemia, hydroxyurea, vaso-occlusive crisis, blood transfusion, hospitalisation

INTRODUCTION

Sickle cell anemia (SCA) is hemoglobinopathy whereinthe the structure, function, or production of hemoglobin (Hb) is affected. It is anautosomal recessive inherited and can range from asymptomatic laboratory abnormalities to loss of life in utero. Sickle cell disease (SCD) is a result of mutation in beta-globin gene that changes the sixth amino acid guanineto valine resulting in Haemoglobin S (Hbs). In India, SCD is a common hemoglobinopathy, next to thalassemia. This variant Hb polymerizes abnormally rendering redblood corpuscles easily deformable, sticky, and shape like a sickle which abnormally adheres to the endothelium of small venules. These abnormal red blood cells (RBCs) promote unpredictable episodes of microvascular vaso-occlusion and premature RBC destruction (hemolytic anaemia). Major clinical features include episodes of ischemic pain and ischemic or frank infarction within the spleen, central nervous system, bones, liver, kidneys, and lungs[1].The prevalence of carrier state of sickle cell varies from 1% to 40% among different tribal groups. Madhya Pradesh has the maximum load with an estimated number of 67,861 sickle homozygote and 9, 61,492 sickle heterozygote. Out of 45 districts in Madhya Pradesh, 27 districts fall into sickle cell belt. The prevalence of sickle cell varies from 10% to 33% in Madhya Pradesh. It has also been estimated that 13,432 pregnancies would be at risk of getting a toddler with SCD in Madhya Pradesh and thus the expected annual births of sickle homozygote would be 3358[2].Although the SCD is present from birth, but symptoms are rarely seen before the age of the 3-6 months with an increased incidence of adverse events coincident with the physiologic fall in fetal Hb (HbF)[3].SCA was first described in south Indian tribal groups and subsequently in central India[4].Vaso-occlusive pain episodes are one of the most common

clinical features associated with SCA[5].Only cure for SCD is Bone Marrow Transplantation,which usually necessitates a human lymphocyte antigen-identical family member donor. Hurdles in thewidespread use of bone marrow transplantation in patients with SCD include a scarcity of suitable bone marrow donors and therefore the got to identify patients with an adequate risk-to-benefit ratio. Due tothese reasons, drug therapy for SCD continues to bethe first and primary mode of disease management that focus speciallyin decreasing the complications of this disease[6].TilldateHydroxyurea, a myelosuppressive agent, is that the only effective drug proven to decrease the frequency of painful episodes. It raises the extent of HbF and thus the Hb level. It was first tested in SCD in 1984. It reduces the rate of painful crisis by 50%. It also reduces the rate of blood transfusions and acute chest syndrome episodes by~50% in adults. It was developed as an anticancer drug and is also been used to treat myeloproliferative disorders-leukemia, melanoma, and ovarian cancer. Side effects; includes anorexia, nausea, vomiting, low absolute neutrophil count (ANC), bone marrow suppression, elevation of liver enzymes, and infertility[7]. The phase 3 NHLBI-sponsored multicentre study of hydroxyurea trial proved clinical efficacy for preventing acute vaso-occlusive crisis in severely affected adults. Based on this cumulative evidence, hydroxyurea has emerged as a valuable therapeutic option for children and adolescents with frequent vaso occlusive events; recent evidence documents sustained long-term benefits with prevention or reversal of chronic organ damage[8].Although questions remain regarding its long-term risks and benefits, the current study is conducted to analyze clinico-hematological response in patients of SCD receiving hydroxyurea.

METHODS

The present study was carried out at MGM medical college Indore from January 2019 to August 2020. After review of synopsis of our research, approval by ethical committee and talking written informed consent from the parents, the patients with SCD were included in the study population.

SOURCE OF DATA

All patients attending Dept. of Paediatrics, M.Y Hospital, Indore and Chacha Nehru Bal Chikitsalaya Evam Anusandhan Kendra,Indore.The study sample was based on the prevalence of SCD, in Madhya Pradesh. Minimal sample size was required in the study was 100.

AIMS AND OBJECTIVES

To study the frequency of vasoocclusive crisis, blood transfusion and hospitalisation/year before and after starting hydroxyurea therapy in children of SCA.

STUDY DESIGN

Retrospective and prospective (ambispective) observational study.

INCLUSION CRITERIA

- Diagnosed cases of SCD by Hb electrophoresis.

EXCLUSION CRITERIA

- Patients <2 years of age.
- HIV reactive patients.
- Patients already on hydroxyurea therapy before enrolment were excluded.

A detailed history, clinical examination, and specific baseline investigations (Complete blood count [CBC], liver function test [LFT], renal function test [RFT], HIV, Hb electrophoresis), were done before starting Hydroxyurea therapy detailed history questionnaire and Medical records used to know age, sex, caste, age of diagnosis, and frequency vaso-occlusive crisis,blood transfusion/year and rate of hospitalisation/per year.The typical starting dose of hydroxyurea was 15-20 mg/kg/day and doses were adjusted according to ANC (target to be to maintained between 2000 and 2500). Then patients were called for follow-up every 2 months till 1 year.On follow-up, frequency vaso-occlusive crisis, blood transfusion/year and rate of hospitalisation/per year was noted.On follow-up specific investigations including CBC, RFT, and LFT done. On each follow up if any, side effects were investigated.If neutropenia <1500/ul and thrombocytopenia <80,000 occurs, hydroxyurea therapy was withhold and monitor CBC with white blood count differentially. When blood counts recover, reinstitute hydroxyurea therapy. Data analyzed as pre-treatment and post-treatment of hydroxyurea therapy.

STATISTICAL ANALYSIS

The data were collected from the proforma of the study and then was compiled in the Microsoft Excel software for the master chart. Statistical Package for the Social Sciences (SPSS) version 22 (IBM SPSS Statistics, Somers NY, USA) was used to analyze data. Chi-square test, Wilcoxon Signed Rank test, Friedman test, and unpaired t-test was used to calculated P-value.

RESULTS

During the study 190 sickle cell patients were recruited for our study.

- Total recruited patients =190
- Lost to follow-up = 106
- Study population at 12 months = 84 (out of which 57 were SCA and 27 were SCD).

Out of 84 patients, 34 were male and 46 were female.
Table 1 shows that the majority of sickle cell patient in our study belong to 6-10 year of age.

Table 1: Age distribution of study population

Age	No of patients	Percent
1-5 year	10	11.9
6-10 year	42	50
11-15 year	24	28.6
>15 year	8	9.5
Total	84	100.0

Following tablessuggests that therapy with hydroxyurea significantly reduces,need for blood transfusion(table 2, figure 1)the frequency of vaso occlusive crisis(table 3, figure 2), rate of hospitalisation(table 4 figure 3)within 1 year follow up (p<0.05).

Table 2: Frequency of blood transfusion/year before and after hydroxyurea therapy

	N	Mean	SD	Minimum	Maximum	95% confidence Interval	P-value
Blood transfusionbefore Hydroxyurea	84	5.36	4.59	0	12	Lower 4.076 Upper6.007	<0.001
Blood transfusion after Hydroxyurea	84	0.32	0.75	0	3		

Table 3: Frequency of vaso occlusive crisis/year before and after hydroxyurea therapy

Variable	N	Mean	SD	Minimum	Maximum		P-value
Frequency of VOC Year Before Hydroxyurea	84	6.43	5.34	0	24.0	Lower 4.87 Upper 7.13	<0.001
Frequency of VOC Year After Hydroxyurea	84	0.43	.66	0	4		

Table 4: Frequency of hospitalization/year before and after hydroxyurea therapy

Variable	N	Mean	SD	Minimum	Maximum	95% confidence Interval	P-value
hospitalization before Hydroxyurea	84	3.52	2.62	.00	12.00	Lower 2.82 Upper 3.95	<0.001
Hospitalization after Hydroxyurea	84	.13	.34	0	1		

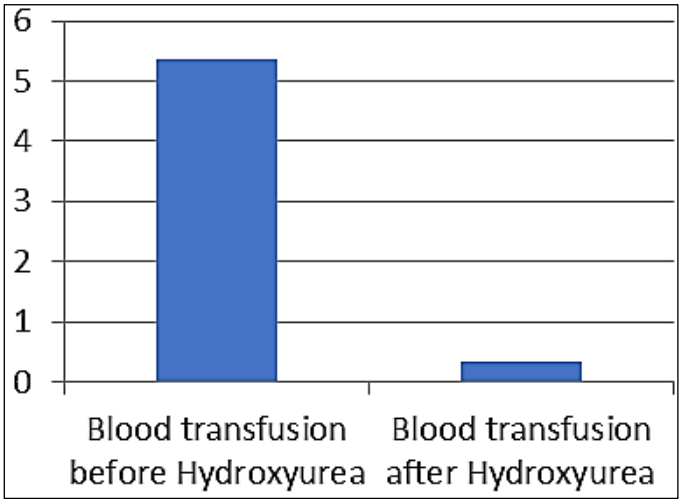

Figure 1: Frequency of blood transfusion a year before and after starting hydroxyurea therapy in sickle cell patient

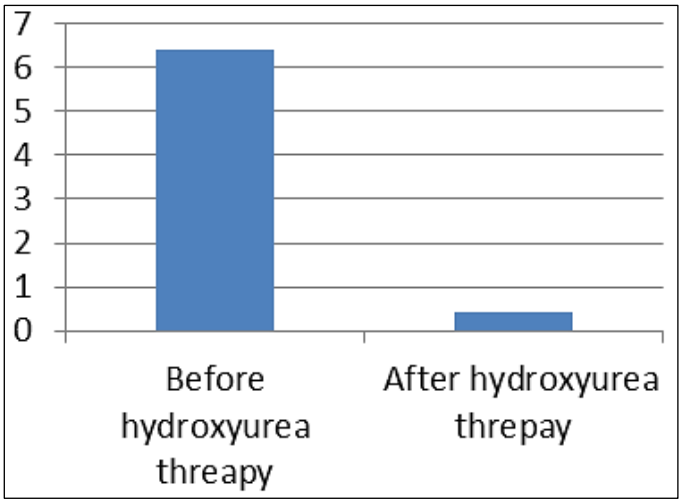

Figure 2: Frequency of vaso-occlusive crisis a year before and after starting hydroxyurea therapy in sickle cell patients

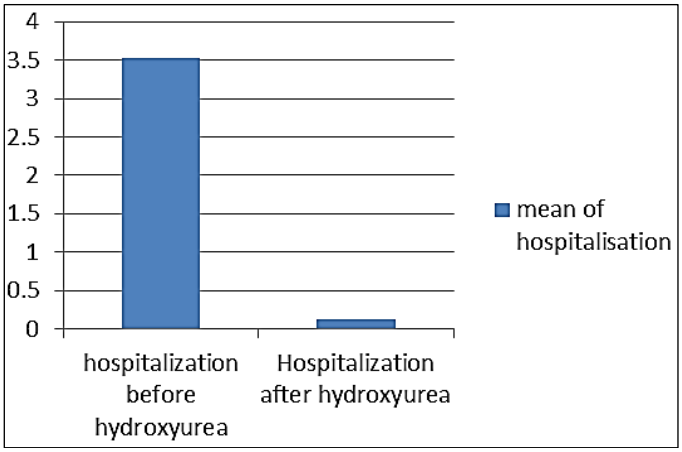

Figure 3: Hospitalisation per year before and after starting hydroxyurea therapy in sickle cell patient

DISCUSSION

Hydroxyurea is a standard and accepted therapy for SCD but is less frequently used in our region and also there are no studies regarding its efficacy and side effects in our native SCD population. So in our study, we used Hydroxyurea as a treatment modality for SCA in order to evaluate its efficacy and safety. A study by Ndefo2 also suggests that although bone marrow transplantation can cure SCD, it is an impractical solution for most Third World countries, which have a high disease burden. Even in the U.S., bone marrow transplantation is limited by the availability of donors. Pharmacological therapies are effective at reducing complications of SCD and are safe and easily administered and they continue to prolong the life expectancy of patients[6].In our present study we observed that Hydroxyurea therapy administered for a period of 1year, it causes significant reduction in the need of blood transfusion in patient of SCD, the decrease in mean value of blood transfusion before and after 12 month Hydroxyurea was from 5.36±4.59 to 0.32±0.75 with P<0.0001.In a study by Jain *et al*., 2013, states that after Hydroxyurea therapy in sickle cell patient for 12 months the need of blood transfusion was reduced by 79.3%[9].In a cohort study by Pondugala *et al*.,[10] in the Hydroxyurea group, mean blood transfusions after 12months was decreased (0.30±0.47 as opposed to entry mean blood transfusions of 2.90±2.93 [P<0.001]). Whereas in the placebo group, there was no difference in mean blood transfusions after 12months (1.90±1.45 as opposed to entry mean blood transfusions of 2.60±3.18 [P=0.283]). This shows that there was statistically significant decrease in number of blood transfusions required, after 12 months treatment with Hydroxyurea (P<0.001) with no significant difference in blood transfusions required in the placebo group who were not given Hydroxyurea therapy (P=0.283)[10].A study by Agrawal *et al*.,[7] (after Hydroxyurea therapy need for blood transfusion decreases by 50%) and Ana Cristina Silva-Pinto I (RBC units transfused decreased from 1.23±2.25 to 0.1±0.3, P=0.0051), similar outcome was observed and it stated that Hydroxyurea decreases the need for blood transfusion[7, 11].This decrease in need of RBC units' transfusion in our study may be due to rise in Hb level associated with Hydroxyurea therapy and decreased hemolysis.

Our study observed that with use of Hydroxyurea therapy administered for a period of 1year, significant reduction in frequency of vaso-occlusive crisis in patient of SCD, the decrease in mean value of blood transfusion before and after 12 month Hydroxyurea was from 6.43±5.34 to 0.43±0.66 with P<0.001. In a study by L. B. Braga *et al*., The number of VOC per year significantly decreased by 80%, from 0.5 ± 0.5 (median 0.4) before starting HU, to 0.1 ± 0.2 (median 0.0) while receiving HU (p = 0.047)[12].Study by Anastasie Nicole alima yanda *et al*., the number of voc per year decreased significantly after 1 year of hydroxyl urea therapy (p<0.05)[13].In a study by Dipti L jain *et al*., The number of VOC per year significantly decreased by 96.4% from4.27 ± 1.99 to0.15 ± 0.47with p value <0.001[14].

Our study also observed that with use of Hydroxyurea therapy administered for a period of 1year, significant reduction in rate of hospitalisation per yearin patient of SCD, the decrease in mean value of rate of hospitalisation before and after 12 month Hydroxyurea was from 3.52±2.62 to 0.13±0.34 with P<0.001. Study by Vivian phan *et al*., In the 2 years prior to uniform HU implementation, hospitalization rate was 0.71 hospitalizations/person-year (122 hospitalizations/86 HU-eligible patients/2 years). In the first 2 years of uniform HU implementation, the rate decreased nearly two-fold to 0.39 hospitalizations/person-year (84 hospitalizations/109 HU-eligible patients/2 years), for a reduction in incidence rate ratio to 0.55 (IRR 0.55)[15].Study by A. ferster *et al*., rate of hospitalisation was significantly reduced with Hydroxyurea(p value 0.0016)compared to use of a placebo(p value 0.47)[16].

LIMITATIONS OF THE STUDY

As the patients come to our setup from distant places, loss to follow up was a major setback because of distance as well as economic constraints for travelling.

CONCLUSION

In our study, we enrolled 121 patients out of which only 84 were able to complete the scheduled follow-up at regular interval of 2 months, i.e., 2, 4, 6, 8, 10, and 12 month. We recorded the baseline value of blood transfusions/year, frequency of vaso occlusive crisis and rate of hospitalisation.We followed the patients at regular interval of 2 months and the above mentioned parameter was compared with the baseline parameter.It was found that there was a significant reduction in the rate of blood transfusion/year, frequency of vaso-occlusive crisis and rate of hospitalisation /year and thus leading to decreased morbidity with prolonged survival[1].So after evaluating the above data, we could conclude that Hydroxyurea is an effective in reducing frequency of blood transfusion in SCA and sickle-β Thalassemia disease. Thus based on the above study, we can recommend regular use of hydroxyurea in our native population at our setup in Indore.

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DECLARATIONS

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CONFLICT OF INTEREST: None.

ETHICAL APPROVAL: Approved by institutional ethical committee.

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