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ORIGINAL ARTICLE

Hydroxyurea in Sickle Cell Disease: Our Experience in Western India

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Abstract Sickle cell disease (SCD) is common in tribal belt of Gujarat, but not addressed effectively as it should be with effective use of Hydroxyurea, supportive care and counseling. In our single centre study of 70 patients of SCD who were only on Folic acid and Blood transfusion support, were analyzed and followed up for 1 year in terms of their clinical symptoms, Blood transfusion requirement, laboratory parameters before and after Hydroxyurea therapy. We found statistically significant improvement in clinical symptoms and positive changes in laboratory parameters studied. This validates the well established role of Hydroxyurea in SCD as seen in the various international trials. Hence it is imperative that the well documented benefits of Hydroxyurea in various International studies should be translated into clinical practice. SCD should be treated like a chronic disorder needing preventive therapy in form of Hydroxyurea and counseling with regular follow up.

Keywords Sickle cell disesase · Hydroxyurea · Pain crisis

Introduction

Sickle cell disease (SCD) is common cause of hereditary hemolytic anemia in Western India. Its effects are seen at a very young age. These people receive frequent blood transfusions thereby exposing them to hazards of transfusion. Complications of SCD vary, ranging from pain episodes which can be treated at home to pain crisis, acute chest syndrome, splenic sequestration syndrome needing hospitalization. Some complications can prove to be life threatening [1]. Microvascular infarcts in different organs can lead to organ dysfunction over a period of time like pulmonary hypertension, cerebral infarcts in SCD patients. In order to decrease the frequency of these complications Hydroxyurea was the first agent to have been tried in SCD. The MSH study results showed that Hydroxyurea is beneficial in preventing and decreasing the complications of SCD [2].

Hydroxyurea is a chemotherapy agent with potent effects on the bone marrow. The agent was used for many years to treat people with certain malignancies before being used for SCD.

In this study 70 SCD patients seen at Hemocare centre Vadodara were followed for a period of 12 months after starting them on HU (started with dose of 15 mg/kg and built up to MTD i.e. maximum tolerated dose till 30 mg/kg with regular monitoring of CBC and keeping a watch for symptoms related to side effects), their clinical presentations and laboratory parameters before starting Hydroxyurea and after 12 months of Hydroxyurea were analyzed to validate the beneficial effects of HU.

Aim and Objective

1) To observe impact of Hydroxyurea 15–30 mg/kg/day single daily dose on quality of life of SCD patients in terms of frequency and intensity of pain episodes, hospitalization and need for blood transfusion.
2) To analyze effect of Hydroxyurea on Laboratory parameters like CBC and HBS and HBF in SCD patients.

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3) To note side effects of long term (up to 1 year) Hydroxyurea.

Materials and Methods

70 HPLC confirmed SCD patients attending the Hemocare centre were included in the study after obtaining informed consent. Patients of all ages and both sex were included. Their HPLC and complete blood count reports before starting the drug follow up CBC reports at 6 months time and at 12 months time after starting HU were noted. HbS and HbF component in HPLC done before treatment and 1 year after on treatment were compared. Due to financial constraints HPLC at 6 months was not done. HB, Total white cell count, Platelet count from CBC at the beginning of Hydroxyurea treatment and after 6 months and 12 months of treatment were compared.

Clinically, patients symptoms before treatment with Hydroxyurea and on treatment with Hydroxyurea were compared. The history of their symptoms, need for hospitalization blood transfusions before Hydroxyurea and on follow up visits was noted down. Self reported pain scales as per following pain score were noted [3, 4]. This helped in understanding the pain symptoms objectively.

Pain Score

Grade 0	No pain
Grade 1	Minimal pain
Grade 2	Pain present but not affecting daily activities
Grade 3	Requiring analgesics but able to carry out daily work
Grade 4	Requiring analgesics but unable to carry out daily activities
Grade 5	Severe pain, requiring hospitalization

Average of each parameter of CBC i.e. Hb, TLC, PLT in concerned age group was calculated at start of Hydroxyurea, at 6 months and at 1 year of Hydroxyurea. Appropriate statistical test (Friedman Annova "F"tests) was applied. Average of HBS and HBF values at 0 and 12 months of HU were tabulated and paired "t" test was applied to see statistical significance. Clinically, number of pain crisis requiring hospitalization per year (average in each group), average pain score as per pain scale mentioned above and frequency of blood transfusion/year required before and after 1 year of HU were tabulated and paired "t" test was applied.

Results

During the 1 year, a total of 70 patients of SCD were studied. Of these 42 were males and 28 were females. 11 patients were from age group 0–10 years (15.71 %), 22 pts (31.42 %) were from 11–20 years, 26 pts (37.14 %) from 21–30 years and 11 pts (15.71 %) from age group 31 years and above.

In Table 1, Hemoglobin of patients in all age groups showed improvement and it was statistically significant. In age group 21–30 years p value was < 0.001. In Tables 2 and 3 decrease in TLC, PLT is noted, however statistically not significant. It was found to be statistically significant only in two group's i.e. 0–10 years and 21–30 years. Average TLC in age group 0–10 years was 14,264/mm at the beginning and at 12 months was 8629/mm. In age

Table 1 Hemoglobin levels of the SCD patients at start of Hydroxyurea treatment and at 6, 12 months of Hydroxyurea treatment

Age group	HB			Friedman Annova 'F' test (p value)
	0	6 months	12 months	
Age 0–10 years	7.66	9.35	9.63	6.65 (0.006)
Age 11–20 years	10.11	10.35	10.90	4.39 (0.01)
Age 21–30 years	9.59	10.15	10.69	14.2 (<0.001)
Age 31 years and above	8.86	10.26	10.98	3.85 (0.04)

Table 2 Total white blood cell count of SCD patients at start of Hydroxyurea and at 6, 12 months of Hydroxyurea treatment

Age group	TC			Friedman Annova 'F' test (p value)
	0	6	12	
Age 0–10 years	14,264	9433	8629	10.86 (0.001)
Age 11–20 years	7726	7447	7775	0.17 (0.84)
Age 21–30 years	9741	8515	7713	5.15 (0.009)
Age 31 years and above	15,415	9348	9180	2.39 (0.12)

Table 3 Platelet count of SCD patients at start of Hydroxyurea treatment and at 6, 12 months of Hydroxyurea treatment

Age group	PLT			Friedman Annova 'F' test (p value)
	0	6	12	
Age 0–10 years	4.18	3.62	3.56	1.86 (0.18)
Age 11–20 years	2.25	1.99	2.15	0.71 (0.49)
Age 21–30 years	3.01	3.21	2.85	2.27 (0.11)
Age 31 years and above	2.91	2.54	2.67	1.78 (0.19)

group 21–30 years it was 9741/mm and 7713 at 12 months. In both cases, the total leucocytes were well within normal range. Similarly the average platelet count in all age group did not show any statistically significant drop. Platelets count is within normal acceptable range.

There is reduction in Total white blood cell counts level in all age group after patients on Hydroxyurea treatment but this reduction is found to be statistically significant on application of Friedman Anova F test, only in age 0–10 years and in age group 21–30 years.

There is reduction in platelet counts level in all age group after patients on Hydroxyurea treatment but on application of Friedman Anova F test, this reduction is found to be statistically not significant in all age groups.

In Table 4 comparison of patients HPLC report at beginning of HU therapy and at 12 months of HU therapy shows reduction in values of HBS and increase in values of HBF and they were found statistically significant.

Clinically patients showed improvement in their symptoms in terms of decrease in their pain episodes which affected their quality of life. The self assessed pain score decreased after patients were started on HU therapy and was statistically significant as evident in Table 5.

Table 4 HPLC (HbS HbF levels) report of SCD patients before starting Hydroxyurea treatment and after 12 months of Hydroxyurea treatment

Age group	HBS levels		Paired t test (p value)
	0	12	
Age 0–10 years	74.88	67.19	3.55 (0.005)
Age 11–20 years	74.42	68.11	9.01 (<0.0001)
Age 21–30 years	77.39	70.25	5.94 (<0.0001)
Age 31 years and above	73.53	64.85	8.26 (<0.0001)
Age group	HBF levels		Paired t test (p value)
	0	12	
Age 0–10 years	14.54	23.22	3.30 (0.008)
Age 11–20 years	17.70	24.70	8.98 (<0.0001)
Age 21–30 years	14.34	23.24	6.67 (<0.0001)
Age 31 years and above	17.50	27.86	7.67 (<0.0001)

Table 7 Average Blood transfusions per year required before Hydroxyurea and Blood transfusion required in the year after starting Hydroxyurea

Age group	BT		Paired t test (p value)
	Before	After	
Age 0–10 years	0.45	0.09	1.49 (0.1669)
Age 11–20 years	0.68	0.09	**2.89 (0.008)**
Age 21–30 years	0.31	0.12	1.99 (0.06)
Age 31 years and above	0.45	0.55	0.24 (0.8)

Table 5 Average pain scores of SCD patients before Hydroxyurea treatment and after starting Hu treatment

Age Group	Gen. pain Score			Paired t test (p value)
	Before	After 12 months	Changes (%)	
Age 0–10 years	2.45	1.27	−47	5.22 (0.0004)
Age 11–20 years	2.95	1.09	−61	8.74 (<0.0001)
Age 21–30 years	2.77	1.12	−58	9.54 (<0.0001)
Age 31 Years and above	2.73	0.90	−64	3.79 (0.004)

Table 6 Comparison of pain crisis episodes in the year before starting Hydroxyurea treatment and in the year after starting Hydroxyurea

Age group	Pain crisis episodes		Change (%)	Paired t test (p value)
	Before	After		
Age 0–10 years	2.91	0.36	−88	9.03 (<0.0001)
Age 11–20 years	3.77	0.55	−84	10.72 (<0.0001)
Age 21–30 years	2.77	0.42	−84	13.41 (<0.0001)
Age 31 years and above	3.18	0.27	−91	9.22 (<0.0001)

There was statistically significant drop in number of pain crisis which required hospitalization as evident from Table 6.

Requirement of blood transfusion was decreased in all patients but statistically significant decrease was noted only in age group 11–20 years as seen in Table 7 (indicated in bold).

Discussion

SCD is common hereditary hemoglobinopathy in western India. As per the Gujarat government site of Sickle cell anemia program in Gujarat, the prevalence in tribal belt of Gujarat is high (30 %). Gujarat has 89.12 lakh tribal population and is expected to have at least 9,00,000 sickle cell trait and 70,000 SCD patients. 30 % of SCD children die before they reach adulthood (14 years) and the remaining 70 % die by the age of 50 years [5]. SCD increases the mortality and morbidity in young productive age group. It not only adversely affects the quality of life of Sickle cell patients but also increases the economical liability. In SCD, the gene defect is a known mutation of a single nucleotide of the β-globin gene, which results in glutamic acid being substituted by Valine at position 6. Hemoglobin S with this mutation is referred to as HbS, as opposed to the normal adult HbA. This is normally a benign mutation, causing no apparent effects on the secondary, tertiary, or quaternary structures of hemoglobin in conditions of normal oxygen concentration but leads to, under conditions of low oxygen concentration, polymerization of the HbS. This causes Hemoglobin S molecules to aggregate and form fibrous precipitates [6]. Variations in the severity of sickle cell disease between individuals usually defy explanation. Some factors have been identified that ameliorate the severity of the condition [7]; however the most important of these is a high level of hemoglobin F (HbF) in the erythrocytes [8]. The first insight into the role of fetal hemoglobin in the clinical manifestations of SCD was made by a pediatrician, Janet Watson. She and her colleagues at a New York hospital noted that babies with SCD rarely had manifestations of the condition in the first year of life. They proposed that the high level of fetal Hb in the red cells, which persists during the first year of life, somehow protects the infant. Fetal Hb levels decline to their routinely low steady-state level between the ages of 1–2 years. The childhood manifestations of SCD are seen thereafter. Patients with SCD who also have hereditary persistence of fetal hemoglobin (HPFH) often have few if any symptoms [9]. In these individuals, Hb F usually comprises greater than 20 % of the hemoglobin in the erythrocytes. Patients may be partially protected from the ravages of SCD with even lower levels of Hb F [10]. Unfortunately; few patients with SCD have Hb F levels of greater than 10 or 11 % in the absence of HPFH. Fetal Hb disrupts the polymerization of deoxy-Hb-S [11].Since polymerization of deoxy-Hb-S is the signal event in the pathogenesis of SCD, fetal Hb effectively prevents disease manifestation. The distribution of Hb F among RBCs is also important. In HPFH, Hb F exists at high levels in all red cells.

Hydroxyurea was used as chemotherapy agent when it was discovered. Due to its ability to increase the HBF levels it was then tried in SCD. The first approved drug for the causative treatment of sickle-cell anemia, Hydroxyurea, was shown to decrease the number and severity of attacks in a study in 1995 [12] and shown to possibly increase survival time in a study in 2003. On January 31, 1995, the multicenter study of hydroxyurea in sickle cell anemia (MSH) was suspended by the NIH because patients on the Hydroxyurea arm of the study had significantly fewer painful crises than did the controls [12]. This made Hydroxyurea the first (and only) drug proven to prevent sickle cell crises [13–15]. A second major observation was that 50 % fewer episodes of acute chest syndrome occurred in the patients treated with Hydroxyurea. Hydroxyurea does not cure SCD, nor is it effective in all patients. A detailed study showed that Hydroxyurea modifies the characteristics of red cells in patients with homozygous HbS disease to resemble those of patients with HbSC disease [16].

The drug also enhances fetal hemoglobin by developing erythroid cells [17]. Since fetal hemoglobin blocks sickling, Hydroxyurea has been administered to patients with SCD in an effort to enhance fetal hemoglobin production [18]. Hydroxyurea induces fetal hemoglobin production, increases the red cell mean corpuscular volume, and reduces the number of dense cells and irreversibly sickled cells in the circulation [19].

Multiple beneficial effects of Hydroxyurea for SCA

(1) Fetal hemoglobin induction through soluble guanylyl cyclase activation and altered erythroid kinetics [20, 21];
(2) Lower neutrophil and reticulocyte counts from ribonucleotide reductase inhibition and marrow cytotoxicity;
(3) Decreased adhesiveness and improved rheology of circulating neutrophils and reticulocytes;
(4) Reduced hemolysis through improved erythrocyte hydration, macrocytosis, and reduced intracellular sickling; and.
(5) Nitric oxide (NO) release with potential local vasodilatation and improved vascular response.

Additional benefits of Hydroxyurea treatment include salutary effects on the circulating erythrocytes. Peripheral erythrocytes undergo numerous morphologic and

physiologic changes during Hydroxyurea dose escalation to MTD, including macrocytosis, increased mean corpuscular hemoglobin, better hydration, more targeting, less hemolysis, and fewer sickled forms. Overall blood flow is improved, with a higher hemoglobin concentration and lower LDH and bilirubin levels. Finally, the Hydroxyurea molecule contains a Nitrous Oxide moiety that can be released directly through unknown metabolic processes [22] Nitrous Oxide has beneficial effects on vascular endothelium, including local vasodilatation, and could help offset proposed hemolysis-related NO consumption [23]. This effect may help explain the clinical improvement some patients feel soon after initiating Hydroxyurea treatment, before reaching MTD with maximal HbF induction.

In our study of 70 patients of SCD not a single patient was on HU before he was referred to Haemocare. In our single centric study of 70 patients, we found the spectrum of clinical presentation very varied. Some patients had symptoms as early as 8 months of age while some became symptomatic only in their second decade. Their blood transfusion requirement was also different. It was observed that severity of symptoms and blood transfusion requirement was not related to the HBS level in HPLC report; however it was observed that patients with high HBF did have lesser symptoms and less number of hospitalizations for pain crisis. On analysis of the lab parameters all SCD patients were anemic with average Hb:8gm %. The low Hb is attributed to continuous hemolysis due to ongoing sickling. As our patients were majority from low to mid social community group, Iron deficiency to some extent may be contributing to toward anemia. On HU therapy, Hb showed improvement in all age group and average Hb of 10 gm % was achieved. HU decreases the rate of sickling and hence contributes to anemia correction.

Major short term complication of HU is decrease in TLC and PLT count [24]. In our study, the TLC and PLT did decrease but did not show significant drop. The TLC and PLT counts were still in normal range and hence HU was not discontinued in any patient. Thus, the low weight adjusted dose of HU did not cause significant myelosuppression as expected. Of course regular CBC monitoring is mandatory to pick up early cytopenias. HPLC at the end of the 12 months showed decreased HBS levels associated with increase in HbF levels. Increased HbF levels have been proved to be beneficial in SCD as mentioned above. It has been shown to decrease polymerization of HbS and thereby decrease the RBC membrane fragility and hemolysis. Clinically this has correlated with decrease in pain scores and pain crisis per year requiring hospitalization and to some extent BT requirement. Also few studies have followed patients of SCD on Hydroxyurea for periods more than 1 year and are encouraging [25].

MSH study conducted in adults above 18 years of age had to be discontinued earlier than planned as the patients on Hydroxyurea arm showed significant symptomatic benefits as compared to the patients on placebo. BABY-HUG, HUSOFT and HUSOFT extended study are the studies which have proven the benefits and safety of HU in pediatrics patients and have also got the similar results.

Being hereditary in nature, SCD has no permanent cure except for bone marrow transplant [26]. Majority of our Sickle cell patients come from tribal belt and have financial constraints. Severity of clinical presentations was also varied in these patients, many patients did not had severe symptoms requiring hospitalization. SCD patients are not absolutely transfusion dependent like Thalassemia patients. They can be managed on HU therapy effectively under supervision with regular follow up CBC reports. The dose of HU can be adjusted as per the clinical tolerance and cytopenias as evident on CBC.

Bone marrow transplant can be offered to SCD patients having HLA matched donor and who can afford it, with its small percentage of risk in expert hands.

Conclusion

Our single centre study validates the beneficial effect of Hydroxyurea in decreasing the sickle crisis and transfusion dependency thereby improving the quality of life of SCD patients.

Benefits of Hydroxyurea should be passed on to maximum number of SCD patient (covering the tribal belt), by starting the drug in patients who become symptomatic due to SCD. This will require patient as well physician sensitization at the periphery as it was our observation that the drug was not regularly used by the physicians and the affected patients.

It can be safely given with regular monitoring of Complete blood count, though we would like to continue to monitor our patients on Hydroxyurea for longer time to note any long term side effects.

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