JIHS The Journal of Integrated Health Sciences

Available online at www.jihs.in

Original Article

Role of Hydroxyurea In Management of Sickle Cell Disease

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ABSTRACT

Introduction: Sickle cell disease is an autosomal recessive chromosomal disorder. The prevalence of the sickle gene in India is found to vary from 2-34%. The clinical syndrome is a result of chronic anemia, and vaso-occlusion, which in turn can give rise to chronic damage. Hydroxyurea is a recommended treatment for sickle cell disease. Hydroxyurea is a myelosuppresive drug and is also indicated for other sickle cell-related complications, especially in patients who are unable to tolerate other treatments.

Materials and methods: All Hb electrophoresis proven sickle cell anemia children of age group between 6 months to 18 years of age coming to the OPD and ward of Pediatrics department of Dhiraj hospital were included in the study. They were subjected to routine investigations and management.

Result: The study was conducted on 70 patients with Hb electrophoresis proven sickle cell disease. After treatment with hydroxyurea for 9 months at mean dose of 25-30 mg/dl, patients improved symptomatically and clinically. Hb electrophoresis at 9 months showed a significant increase in mean HbF levels.

Key words: sickle cell disease, hydroxyurea, efficacy.

INTRODUCTION

Sickle cell disease is an autosomal recessive chromosomal disorder, where the blood cells contain abnormal sickle shaped hemoglobin (HbS).

The highest frequency of sickle cell disease is found in tropical regions, particularly Sub-Saharan Africa, India and the Middle-East. The prevalence of sickle cell anaemia is highly common in the tribal- belt of Central and Southern India. The prevalence of the sickle gene in India is found to vary from 2-34%[1,2]. Prevalance of sickle gene is found to be 0-18% in north eastern India, 0-33.5% in western India, 22.5-44.4% in central India and 1-40% in southern India and the gene frequency of HbS varies between 0.031-0.41[3]. According to recent survey by ICMR the incidence of sickle cell disease is the highest among tribals, in the state of Gujarat

The clinical syndrome is a result of chronic anemia, and vaso-occlusion, which in turn can give rise to organ damage. The most common clinical problem is a painful vaso-occlusive crisis, which causes over 90% of acute hospital admissions and significant morbidity in the community[4].

The red cell adheres to the endothelium through a series of mechanisms, either directly via exposed red cell membrane phophatidylserine or sulfated glycans, or by using soluble adhesion

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molecules (e;g. integrins and thrombospondin and / or high molecular weight von willebrand factor) as a bridge. Adherent leucocytes and red cells, narrow the diameter of the blood vessel, slowing blood flow and trapping dense sickled cells. The increase in blood transit time also increases red cell sickling, and finally , blood vessel occlusion occurs. This produces ischemia and finally necrosis, which causes cytokine release and perpetuates the sickle event.

Hydroxyurea is a recommended treatment for sickle cell disease. Hydroxyurea is a myelosuppresive drug and is also indicated for other sickle cell-related complications, especially in patients who are unable to tolerate other treatments. In patients who either will not or cannot continue blood transfusion therapy to prevent recurrent stroke , hydroxyurea therapy, maybe, a reasonable alternative. The typical starting dose of hydroxyurea is 15-20mg/kg given once daily, with an incremental dosage increase every 8 week of 5 mg/kg, and if no toxicities occur, upto maximum of 35mg/kg per dose.

METHODOLOGY

This was a prospective observational study conducted in patients coming to OPD or admitted in ward of Pediatrics department of Dhiraj hospital.

Inclusion criteria:

1. All the Hb electrophoresis proven sickle cell anemia children between age of 6months to 18 years.

Exclusion criteria:

1. Children with sickle cell trait, sickle beta thalessemia and other heterozygous sickle combinations.
2. Serum creatinine above the upper limit of the normal range.
3. Serum alanineaminotransferese more than twice the upper limit of normal for age.
4. Parents not willing to give consent.

All the subjects were subjected to routine investigation and were monitored regularly on follow up.

RESULT

Total 70 patients who were tested for sickling positive and subjected to Hb electrophoresis were enrolled in the study, out of which 36(51.4%) patients were above the age of 10 years and mean age of presentation in the study was 10.24 years for male patients and 10.27 years for female patients. Out of total 70 patients 37 (52.9%) were males and 33(47.1%) were females (Table 1).

Table 1. Age and sex wise distribution of cases

Age/ sex	No of cases (n=70)
>10 yrs	36 (51.4%)
5-10 yrs	30 (42.9%)
<5 yrs	4 (5.7%)
Male	37 (52.9%)
Female	33 (47.1%)

Out of total 70 patients majority of the patients belonged to scheduled caste, highest being Bhilala 14 cases (20%), followed by Rathwa 10 cases (14.3%) , Bhil 5 cases (7.1%) and there were 26 cases (37.14%) belonging to other castes (Table 2).

Out of total 70 cases, 28 cases were reported in rainy season i.e. from July to September and 26 patients were reported in winter season (Table 3).

Pre and post hydroxyurea comparison of blood transfusion requirements in sickle cell positive patients showed that after treatment with hydroxyurea only 4 (5.71%) patients required transfusion once, 1 (1.43%) required transfusion 2-4 times and 0 (0%) required more than 4 times as compared to the requirement before hydroxyura i.e. 17 (24.29%) required 1 time, 21

(30%) required 2-4 times and 4 (5.71%) cases required more than 4 times. (Table 4)

Table 2. Caste wise distribution of cases

Cast	No. of cases (n=70)
Bhilala	14 (20%)
Rathwa	10 (14.3%)
Bhil	5 (7.1%)
Chauhan	5 (7.1%)
Parmar	5 (7.1%)
Vasava	5 (7.1%)
Others	26 (37.14%)

Table 3. Month wise distribution of sickle cell patients

Month	No. of cases (n=70)
January	7 (10.0%)
February	4 (5.7%)
March	7 (10.0%)
April	1 (1.4%)
May	10 (14.3%)
June	4 (5.7%)
July	11 (5.7%)
August	11 (15.7%)
September	9 (15.7%)
October	1 (1.4%)
November	0 (0%)
December	8 (11.4%)
Total	70

Table 4. Pre and Post Hydorxyurea comparison of blood transfusion requirements

Blood Transfusion	Pre (n=70)	Post (n=70)
1	17 (24.29%)	4 (5.71%)
2-4	21 (30%)	1 (1.43%)
>4	4 (5.71%)	0 (0%)

After treatment with hydroxyurea only 9 (12.8%) patients required hospital admission once, 2 (2.86%) required admissions 2-4 times and none were admitted for more than 4 times as compared to number of hospital admissions before hydroxyurea treatment i.e. 15 (21.43%), 27(38.57%) and 3 (4.26%) respectively (Table 5).

Table 5. Pre and Post hydroxyurea comparison of hospital admissions

Hospital stay	Pre (n=70)	Post (n=70)
1	15 (21.43%)	9 (12.86%)
2-4	27 (38.57%)	2 (2.86%)
>4	3 (4.26%)	11 (5.71%)

Table 6. Pre and post hydroxyurea comparison between mean hemoglobin and mean neutrophil count

Hemoglobin	Mean
Pre	8.478
Post	9.478
Neutrophil count	
Pre	7.784
Post	4.132

Mean hemoglobin before hydroxyurea treatment was 8.48 mg/dl and after treatment was 9.48mg/dl. Mean neutrophil count before treatment was 7780/m^3 and after treatment was 4130/m^3, it showed significant decrease in neutrophil count after treatment (Table 6).

Table 7. Pre and post hydroxyurea comparison between mean HbF values:

HbF values	Mean
Pre	18.977
Post	24.705

It shows that mean HbF value before hydroxyurea is 18.9% and post hydroxyurea treatment is 24.7% (Table 7).

DISCUSSION

This study was conducted on the patients visiting the Department of Pediatrics, Dhiraj hospital. All the patient who tested positive for sickling by the solubility test were subjected to Hb Electrophoresis. The patients showing the

presence of band representing HbS in the Hb electrophoresis were further categorized as SCD-SS, SCD-beta-thal and sickle cell trait depending upon HbS and HbA2 levels. Patients with SCD-SS were included in the study and were started on hydroxyurea. Regular hematological studies were done on follow up and repeat electrophoresis was done at 9 months. Most of the patients presented between 7-12 years of age with mean age of presentation 10 years. Similar results were found in other studies conducted by other authors such as Sahu et.al.[5], Patel.et.al.[6], Deore et.al.[7]. Majority of the patients (91.5%) belonged to scheduled castes, scheduled tribes and other backward classes with only 8.5% belonging to the upper caste. A higher prevalence of sickle cell disease among tribal communities was also shown by similar studies in the past such as Balgir RS et.al.[8], Kaur et.al.[9], Deore et.al.[7], Patra et.al.[10], Mohanty et.al.[2] who found that incidence of crisis is increased in rainy season followed by winter season, which co-relates with our study. Gulbis et.al.[11] had similar results on hematological and clinical profile. The majority of patients no longer experienced vaso-occlusive crises requiring hospitalization during the first year of hydroxyurea treatment. HbF increased from 3% to 14% and Hb 8.2gm/dl to 8.7gm/dl. Significantly low rate of hematological toxicity was observed. Jain et.al.[12] conducted a similar study in 2013 and had results similar to our study, i.e. there was significant rise in HbF levels from 16.45% to 21.98%.

CONCLUSION

The study was conducted on patients with sickle cell disease who were evaluated for their clinical and hematological profile and role of hydroxyurea in its management. It was observed that treatment with hydroxyurea resulted in a clear clinical benefit , with a significant reduction in the number of blood transfusions and hospitalisations. There was an associated improvement in HbF%. No clinically or hematological relevant toxicity was associated with hydroxyurea therapy. The outcome of the present study and the available evidences recommended a wider adoption of hydroxyurea for treatment in high prevalence areas. At the current time, curative therapy with stem cell transplantation remains an unavailable option to most patients with SCA. Until something better becomes available that has a wide spectrum of efficacy and safety, hydroxyurea appears to be the best available treatment option for children and adolescents with SCA.

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