ORIGINAL RESEARCH PAPER

Paediatrics

CLINICAL PROFILE AND MID-TERM OUTCOME OF CHILDREN WITH SICKLE CELL DISEASE TREATED WITH HYDROXYUREA

KEY WORDS: Sickle Cell Disease, Hydroxyurea, Hb electrophoresis, Haemoglobin F

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ABSTRACT

Objective: To study the clinical profile of patients with Sickle cell disease (SCD) and effect of Hydroxyurea (HU) on their haematological and biochemical profile. **Method:** This prospective observational study included children with Hb Electrophoresis proven SCD presenting in OPD or admitted in ward from November 2012 to May 2014. After detailed history, examination and baseline haematological and biochemical profile, Hydroxyurea was started and gradually increased. Primary outcome was reduction in symptoms, blood transfusion and hospital admissions. Secondary outcome was improvement in haematological and biochemical profile including Hb electrophoresis. **Result:** Study population included 70 patients with SCD with median age of 10.2 (2-18) years. Maximum children (91.5%) belonged to tribal population . Most children presented with body ache(70%) followed by abdominal pain(41.4%) and fever(34.3%). During 9 months of treatment with HU there was 81.4% decrease in clinical symptoms and significant reduction in hospital admissions(P<0.0001) and blood transfusions(P<0.0001). mean haemoglobin was increased to 9.4 mg/dl and there was significant improvement in Hb electrophoresis, mean Haemoglobin F (HbF) increased to 24.70% with P<0.0001. **Conclusion:** In patients with SCD, treatment with hydroxyurea is associated with favourable short-term and mid-term outcomes.

INTRODUCTION

Sickle cell disease is the family of haemoglobin disorders inherited in a Mendelian recessive manner in which a sickle β-globin gene is inherited . The most common type is sickle cell anaemia , the homozygous situation (SS) while other compound heterozygous situations occur featuring the same clinical problems . In 1952 , Lehman and Catbush reported the presence of the disease among the tribals of Nilgiri hills for the first time [1] . The prevalence of sickle gene in India is found to vary from 2-34% [1,2] . SCD is predominantly found in central India i.e. Maharashtra , Madhya Pradesh , Orissa , Andhra Pradesh and Gujrat . The clinical syndrome is the result of chronic anaemia and vaso-occlussion , which in turn can give rise to chronic organ damage . Death in SCD is either caused by chronic organ failure or an acute catastrophic event such as a stroke , acute chest syndrome , splenic sequestration or other complications . Hydroxyurea (HU) is a chemotherapeutic agent which is now considered as the main pharmacological agent capable of preventing complications of SCD and improving the quality of life in SCD .The efficacy of HU in the treatment of SCD is generally attributed to its ability to increase HbF [3] . Most studies in children have used doses of approximately 20 mg/kg/day . The most common side-effect is dose dependent myelosuppression which is usually transient [4] . HU has been approved both by Food and Drug Administration (in 1999) and European Medicines agency (in 2008) for children and adults with SCD .

METHODS

This prospective observational study was conducted in a 1000 bedded tertiary care hospital situated in rural area of Vadodara , Gujarat over a period of one and a half year (November 2012- May 2014) following approval from our institutional committee.

All Hb electrophoresis proven SCA children (male and female) between ages 6 months to 18 years were included in the study . Children with age less than 6 months or with sickle cell trait , sickle β thalassemia and other heterozygous sickle combinations were excluded from the study . Serum creatinine above the upper limit of normal for age or serum alanine aminotransferase more than twice the upper limit were also criteria for exclusion .

All the suspected patient who tested positive for sickling by the solubility test were subjected to Hb Electrophoresis (citrate agar gel) . The patients showing the presence of band representing HbS more than 50% were labelled as SCA and were enrolled in the study . A detailed history and clinical examination including anthropometry of enrolled children were done as per the pre-structured Performa . Baseline haematological and biochemical investigations (complete blood count , reticulocyte count , SGPT , creatinine and LDH) were done at the time of enrolment .

Hydroxyurea was started at an initial dose of 20 mg/kg/day and was gradually escalated at 5 mg/kg/day every 8 weeks to a maximum dose of 30-35 mg/kg/day for maximal benefits . Study visits occurred every month for first three months and then at 6th month and 9th month . At each visit laboratory and clinical efficacy parameters , as well as potential adverse effect history were collected and dose modification was done.

In case of haematological toxicity which was defined as absolute neutrophil counts <1500/mm^3 , platelet count < 80,000/mm^3 and ALT elevated more than twice the upper limit for age , HU was discontinued until counts recover (usually within 1 week) . HU was restarted with reduction in dose by 2.5 – 5.0 mg/kg/day .

STATISTICAL ANALYSIS : Data was entered in MS Excel and analysed using SPSS 20 . Paired t test was used for comparison of means . Categorical variables were compared using nonparametric tests .

RESULTS

A total of 198 patients suspected to have sickle cell disease based on clinical presentation were subjected to sickling solubility test . Out of which 115 patients tested positive and were subjected to Hb electrophoresis . 77 patients were diagnosed as sickle cell anaemia (HbS>50%) based on the reports and were included in the study . They were started on HU and regular haematological studies were done on follow up . 70 patients completed the study , 3 were loss to follow up and 4 patients had poor compliance to the medication .

Out of 70 patients , 37 were male and mean age of presentation was 10.24 years . Majority of the patients(91.5%) belonged to schedule castes and schedule tribes , highest being Bhilala , Rathwa and Bhil. Maximum number of patients (40%) reported in the rainy season (from July till September).

Table 1 shows clinical characteristics of SCA patients ,with body ache being the most common symptom followed by abdominal pain and fever. 84.3% patients were found to be pale and 41.4% had splenomegaly. 42 patients had received blood transfusion at least one time in the past and all the patients were admitted once or more previously.

Table 1 Clinical and haematological profile of patients with SCA (*N*=70)

Characteristics	No.(%)
Symptoms	
Body ache	49(70)
Abdominal pain	29(41.4)
Fever	24(34.3)
Joint pain	20(28.6)
Weakness	14(20)
Chest pain	02(2.9)
Signs	
Yellowish discolouration of eyes	10(14.3)
Splenomegaly	29(41.4)
Hepatosplenomegaly	17(24.3)
Blood transfusions	
2 or more	26(35.7%)
Previous hospital admission	
2 or more	30(42.9%)
Mean hemoglobin	8.47 mg/dl
Mean leucocyte count	12,618/mm
Hemoglobin electrophoresis	
HbS	78.42%
HbF	18.97%
HbA2	2.61%

*the total number of symptoms are more than total no. of patients because there were more than one symptom in many patients.

Table 2 shows comparative clinical and haematological features post treatment with HU for 9 months. When compared to the event rate before initiation of HU , there was a significant decrease in the frequency of vasoocclusive crisis (decrease by 81.4%) , sequestration crisis and acute chest syndrome. None of the subjects had acute chest syndrome and sequestration crisis after initiation of HU. Requirement of blood transfusion decreased by 88.09% and that for hospitalisation by 75.55% .

Haematological parameters were compared using Paired T test . There was a significant increase in mean haemoglobin (9.48%) with p value <.000 . Also there was a significant decrease in total leucocyte count and reticulocyte count. HbF levels were raised significantly from the baseline (18.97%) to 24.70% . There was a marked decrease in HbS levels from 78.42% to 73.41% with p value of <.0001 .

The only toxic effect detected from HU therapy was mild to moderate neutropenia. In this study only one patient had neutrophil count <1500/mm3 that required stopping of drug for a week and then was restarted after recovery with reduction in dose by 2.5mg/kg/day.

Table 2 Shows the comparison between clinical parameters Pre and Post HU (duration: 9 months before and after the treatment). Unit of analysis is no. of events

Clinical parameter	Pre value(%)	Post value(%)	% decrease /increase	Z value(p-value)
No. of patients with complaints	70	13	↓81.4	
Blood transfusion requirement	42(60)	05(7.14)	↓88.09	7.99(<0.0001)
Hospital admission	45(64.29)	11(15.71)	↓75.55	6.76(<0.0001)
Mean haemoglobin	8.47	9.47	↑11.80	(<.000)
Mean total leucocyte count	12,618	8130	↓35.56	(<.000)
Retic count	3.10	1.52	↓50.96	(<.000)
Mean HbS	78.42	73.41	↓6.38	(<0.001)
Mean HbF	18.97	24.70	↑30.20	(<0.001)

DISCUSSION

The present study reports favourable clinical and haematological outcome of treatment with HU at 20-30 mg/kg/day dose in Indian SCA children . Many long term studies have clearly demonstrated the efficacy of HU in African children with SCA . But there are very few studies which have reported the efficacy of HU in Indian children with SCA who have higher HbF compared to other population group .

Clinical experience has been gathered for past two decades regarding the safety and efficacy of hydroxyurea therapy for patients with SCA. The HUG-KIDS STUDY[5] 1999 , which included children aged 5-15 years had similar findings as that of our study . There was significant increase in haemoglobin concentration and HbF with 1 year treatment of HU . No life threatening clinical adverse effects were seen which is similar to our study where only one event of severe neutropenia was seen which recovered on its own in a week of stopping HU .

Singh et al. 2010 [6], conducted a small scale study with 27 patients and found significant increase in HbF from 12.83% to 19.17% similar to the current study . He also observed marked decrease in hospitalisation of patients with SCA over a period of one year which is again similar to the results we had with 75.5% decrease in admission rates.

Studies like BABY HUG trial[7] 2010 and one conducted by Lobo et al.[8] showed significant decrease in pain episodes , dactylitis , hospitalisation and transfusions. Overall survival and quality of life was better in children treated with HU . The phase ½ HUSOFT[9] trial reported that infants tolerate hydroxyurea liquid formulation without any short-term adverse effects and have substantial laboratory and clinical benefits. Similarly the TWiTCH[10] trial results document the efficacy of hydroxyurea therapy for a cohort of children with SCA at high risk for primary stroke.

In the present study we included children aged rate and 6 months to 18 years and after 9 months of treatment with HU at 25-30 mg/kg/day patients improved symptomatically with 81.4% decrease in complaints,75.55% hospital admission rate and 88.09% decrease in blood transfusion rate. Post treatment mean Hb improved (9.4 mg/dl) and there was decrease in total leucocyte count , platelet count and reticulocyte count (decreased to 1.5%). Hb electrophoresis at 9 months showed a significant increase in mean HbF from 18.9% to 24.7% and mean HbS decreased to 73.41%. There was no major side effect.

CONCLUSION

In last few years numerous scientific discoveries are been made in the field of SCD. In our study, treatment with HU resulted in a clear clinical benefit, with significant reduction in number of blood transfusions and hospitalisations. There was an associated improvement in HbF% . No clinical or haematologically relevant toxicity was associated with the HU therapy. The outcome of the present study and the available evidences recommend wider adoption of HU for treatment in high prevalence areas. At the time , curative therapy with stem call transplantation is available to a limited number of patients. Until something better becomes available that has similar wide spectrum of efficacy and safety , HU appears to be the best available option for children and adolescents with SCA.

Limitations Of Study

Being a hospital based study the number of patients recruited were limited . There were no controls taken for the study and patients with sickle-thalassemia combinations were not included in the study.

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