ORIGINAL RESEARCH PAPER
Volume - 10 | Issue - 06 | June - 2021 | PRINT ISSN No. 2277 - 8179 | DOI : 10.36106/ijsr
INTERNATIONAL JOURNAL OF SCIENTIFIC RESEARCH

"EFFICACY OF HYDROXYUREA IN PATIENTS OF SICKLE CELL DISEASE IN PAEDIATRIC AGE GROUP-AN OBSERVATIONAL STUDY"

Paediatrics

Dr. C.M. Bokade Professor and HOD, Dept. of Paediatrics, IGGMC, Nagpur.

Dr. Ketaki Nawlakhe* Senior Resident, Dept. of Paediatrics, IGGMC, Nagpur.*Corresponding Author

Dr. Nikita Singh Senior Resident, Dept. of Paediatrics, IGGMC, Nagpur.

Dr. Bharat Kumar Senior Resident, Dept. of Paediatrics, IGGMC, Nagpur.

ABSTRACT

Aims and objectives: There have been few studies on the efficacy of hydroxyurea in children hence this study was designed for evaluation for efficacy of hydroxyurea in the pediatric age group.

Materials and methods: It was a prospective observational study with a total of 50 patients of SCD which were given hydroxyurea 10mg/kg and were followed up for a period of 2 years for any toxicity.

Results: In this study, majority of cases 20 (40%) were from 9 to 12 years of age group. 26 (52%) were males and 24 (48%) were females. 48 completed the follow up and 2 cases did not complete the follow up visits over a period of 2 years. In this study, SCD related clinical events-frequency of acute painful events and requirement of blood transfusion rate were significantly reduced after hydroxyurea therapy at the end of 2 years when compared with before hydroxyurea therapy with significant p value 0.017 and 0.005 respectively.

Conclusion: Hydroxyurea is an efficacious medicine in the treatment of sickle cell disease in paediatric age group.

KEYWORDS

Hydroxyurea, sickle cell disease

INTRODUCTION:

Sickle cell disease is one of the most common hemoglobinopathies in world and in India caused due to DNA mutation with beta globin gene. SCD affects mainly the African descendents and is spread all over the world as a result of migration. The Central-West Africa, East Asia and India are the most SCD prone regions of the world (WHO report, 2006)[1]. For sickle cell disease there are about 25,00,000 carriers of the gene (Hemoglobin AS) and about 1, 25,000 patients of sickle cell disease in India[2].

In Central India prevalence of Sickle cell is 22.5-44.4%[3]. Prevalence of sickle gene is found to be 0-18% in North Eastern India, 0-33.5% in Western India, 1-40% in Southern India[1].

Hydroxyurea, the only disease-modifying drug for SCD approved by U.S. Food and Drug Administration (FDA), has been well demonstrated in clinical trials to alter the clinical course in SCA. It has shown to decreases rates of pain, dactylitis, acute chest syndrome (ACS), transfusions and hospitalizations, improves quality of life and decreases mortality. The clinical benefits of hydroxyurea were also associated with predictable laboratory benefits, including improvements in hemoglobin concentration, MCV, and HbF levels, along with reductions in WBC count (especially neutrophils), absolute reticulocyte count, and measures of hemolysis. There have been few studies on the efficacy of hydroxyurea in children hence this study was designed for evaluation for efficacy of hydroxyurea in the pediatric age group.

METHODOLOGY

It was a prospective observational study conducted in the department of Paediatrics in a tertiary care teaching hospital in central India from November 2017 to October 2019. Children in the age group of 5-18 years having any one of the following were included in the study:

1. Frequent pain crises (≥2 per year)
2. Acute chest syndrome
3. Avascular necrosis of head of femur
4. Central nervous system event at least once
5. Blood transfusion (≥ 3per year)

EXCLUSION CRITERIA for CASES

1. Cases of sickle cell disease (homozygous) age < 5 Years and > completed 18 years

Sample size:

Considering the expected toxicity- thrombocytopenia which was 8.3 % (Thomas R. Kinney et al 1995) with absolute error 8%, desired confidence interval (1-α)= 95%, minimum sample size required 45 + 10 % lost to follow up. Total sample size required is equal to 50. All the patients enrolled in the study, were treated with hydroxyurea with the minimum dose 10mg/kg/day once daily as fixed dose therapy. They were followed up every 2 monthly for hydroxyurea toxicity for 2 years.

RESULTS:

Total 50 patients of homozygous Sickle cell disease (SS pattern) between age group 5 to 18 years were enrolled and treated with hydroxyurea therapy. In this study majority of cases 20 (40%) were from age group 9-12 years and 16 (32%) cases were from 5-8 years age group and 14 (28%) were from 13-18 age group. Out of 50 patients, 26 (52%) cases were male and 24 (48%) were females.

Indication of starting hydroxyurea in 16 (32%) cases was acute painful crisis, in 14 (28%) patients was frequent blood transfusion (28%), in 9 (18%) patients because of stroke, in 6 (12 %) patients was spleenic sequestration, in 5 (10%) patients was episodes of acute chest syndrome.

The mean acute painful events, mean rate of blood transfusion before hydroxyurea therapy was 1.18 ± 1 SD per year per person and at the end of two years was 0.68 ± 0.82 SD per year per person and it was statistically significant (p=0.005).

The mean stroke events, mean acute chest syndrome as well as spleenic sequestration, mean days of hospitalization and the occurrence of bacterial sepsis before hydroxyurea therapy and on follow up at the end of 2 years was statistically significant ($p<0.05$). The mean haemoglobin (gm/dl), mean MCV (fl), mean reticulocyte count (%) and mean HbF (%) before starting hydroxyurea and at the end of 2 years was statistically significant ($p<0.05$).

DISCUSSION:

Sickle cell disease is one of the most common hemoglobinopathies spread all over the world and in India which is associated with high morbidity and mortality. Curable treatment available is successful Hematopoietic stem cell transplantation or gene therapy with transuded autologous stem cells establishing complete or partial erythropoesis. Only disease modified drug approved by US FDA is Hydroxyurea in adults and children as well.

In this study the age group was 5 to 18 years of either sex. While age group selected in other studies were as follows.

The studies done by Kinney TR et al,[4] Akinyemi O.D. Ofakunrin et al[5] and Suzette O. Oyeku et al[6] had included the age group similar to age group selected in our study.

In our study, out of 50 cases, majority of cases i.e. 20 (40%) cases were from age group of 9 to12 years, 16 (32%) cases were from age group of 5 to 8 years, and 14 (28%) cases were from 13 to 18 age group.

In the present study, most common indication to start hydroxyurea therapy in severely symptomatic sickle cell disease was frequent acute painful events and need of frequent blood transfusion, very few cases of stroke, acute chest syndrome, spleenic sequestration in preceding one year. While in other similar studies, various indications to start hydroxyurea therapy were as follows.

Charache et al[7] included adults with sickle cell anaemia having ≥3 vaso-occlusive crisis per year

Kinney TR et al[4] enrolled severe sickle cell disease children with severe sickle cell disease which was defined as ≥ 3 pain events within the previous year or at least 3 episodes of acute chest syndrome (ACS) requiring hospital admission within 2 years of entry or any combination of 3 episodes of ACS or painful events as an indication to start hydroxyurea therapy

In our study, there is significant reduction in acute painful events per year per person after 2 years of hydroxyurea therapy. (p=0.017)

In our study, there is statistically significant reduction in rate of blood transfusion per year per person and mean days of hospitalization per year per person after 2 years of hydroxyurea therapy. (p=0.005, p=0.027 respectively)

A significant reduction in acute painful events and blood transfusion rate, was also observed in the studies performed by Kenney TR et al[4], Youssry I et al[8], Ersi Voskaridou et al[9], Italia K et al[10], Patel D.K. et al[11], Akinyemi O.D. Ofakunrin et al[5].

In this study there was significant reduction in events of spleenic sequestration, stroke and acute chest syndrome after 2 years of hydroxyurea therapy.

Acute chest syndrome was significantly decreased in Maa-Ohui Quarmyne et al[3], Youssry et al[7], Akinyemi O.D. Ofakunrin et al[5].

There was significant increase in HbF levels percentage, hemoglobin levels and MCV levels after 2 years of hydroxyurea therapy.

Italia K. et al[10],Maa-Ohui Quarmyne et al[3], Youssry et al[8], Patel D.K. et al[11], in their study had shown the significant increase in HbF and MCV levels after hydroxyurea therapy.

In our study, the adherence to hydroxyurea therapy for 2 year duration was assessed by Modified Morisky Scale and the score was 0.31. In Modified Morisky Scale, score of ≤1 indicates good adherence and score of ≥2 indicates poor adherence to hydroxyurea therapy.

Tables:

Table 1: Age and sex wise distribution of cases:

Demographic characteristics		Number	Percentage
Age (years)	5-8	16	32
	9-12	20	40
	13-18	14	28
	Total	50	100
Sex	Males	26	52
	Females	24	48
	Total	50	100

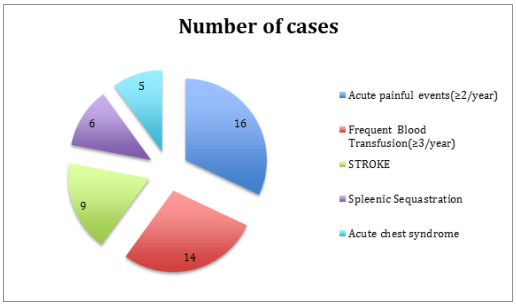

Figure 1: Clinical indications to start hydroxyurea therapy:

Table 2: Comparison of laboratory parameters of the cases before and after hydroxyurea therapy in sickle cell disease:

Laboratory parameters	Before hydroxyurea therapy Cases (n=48)		After hydroxyurea therapy Cases (n=48)		P value
	Mean	SD	Mean	SD	
Hemoglobin (gm/dl)	8.23 (4.5-10.8)	1.39	9.43 (5.89-12.1)	1.27	0.00001
MCV (fl)	74.03 (59.6-88.2)	7.357	78.2 (59.2-90.4)	7.26	0.0045
Reticulocyte count (%)	11.10 (5-17)	3.47	8.4 (2-13)	2.43	0.00004
HbF (%)	19.62 (10.9-31.9)	4.73	22.05 (13-34)	5.73	0.00038

CONCLUSION:

Hydroxyurea is an efficacious medicine in the treatment of sickle cell disease in paediatric age group.

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