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Hydroxyurea in Managing Sickle Cell Anemia in Context of Hematological and Clinical Improvement along with Its Side effects

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Abstract

INTRODUCTION
Sickle cell disease (SCD) is a group of condition with abnormality in the β-globin gene. It ranges from homozygous condition affecting both gene for β-globin to other genotypes like sickle-cell/β^+ thalassemia (HbS/β^+), heterozygous sickle-cell/β^0 thalassemia (HbS/β^0), sickle-cell/haemoglobin C disease (HbSC), and other less occurring genotypes. Hydroxyurea is one of such drug which induces HbF production and was approved by US-FDA for SCA. It is basically a chemotherapeutic agent used for cancer patient and treatment of HIV. Later on its effect on HbF was discovered

MATERIALS AND METHODS
The current study was a prospective hospital based observational study was carried out in the Department of Paediatrics, Institute of Medical Sciences and SUM hospital, Bhubaneswar. All the paediatric population between age group of more than one year to less than 15 years diagnosed with sickle cell anaemia were our study population. A minimum sample of 29 subject was adequate to achieve required power in the study. For the purpose of the study we considered 30 subjects to be included in the study.A valid consent was taken from the parents (and children where applicable) before enrolling to the study. Hydroxyurea was started at dose of 20mg/kg in the children; and was increased gradually 5mg/kg every eight weeks of therapy to maximum tolerable dose (up to 35mg/kg).

RESULTS
Mean weight of the children at enrollment was 19.67 ± 4.29 kilograms while the mean height was

108.7 ± 7.94 cm. The baseline characteristics of the study population. We also compared the proportion of subject experience specific complications before and after the therapy and compared them. The proportion of subject experience symptom of vaso-occlusion was 60% before therapy which declined to 30% after therapy. This difference in proportion was statistically significant (P value = 0.035). Similarly, we found a significant decrease in proportion of subject with acute chest syndrome, blood transfusion and hospitalization with a p value of <0.05. The side effect profile of the hydroxyurea. Most common side effect was gastrointestinal problem followed by rash (16.7%). Only few subject showed skin pigmentation (6.67%). Appetite among the children was improved from 46.7% before therapy to 66.7% after hydroxyurea therapy. This change in proportion was statistically significant (P value = 0.034).

CONCLUSION

Hydroxyurea therapy is an effective mode of treatment for children with sickle cell anemia. Hydroxyurea is one such therapy which can reduce the complication or painful crisis in patient suffering from sickle cell anemia and also Hydroxyurea reduces number of hospitalizations, and blood transfusions. Using Hydroxyurea in children suffering from with sickle cell anemia cause raise in Hemoglobin levels, with decrease in HbS and increase in HbF level significantly.

Keywords: Sickle cell disease, Hydroxyurea, Hemoglobin.

INTRODUCTION

Sickle cell disease (SCD) is a most common monogenic inherited disease affecting more than 10,00,000 people in India and millions worldwide [1]. Sickle cell hemoglobin was first described in India by Lehman and colleagues specially in tribal population of Nilgiri hills. Since then, many studies had been conducted and screened for sickle cell gene. The studies showed a high prevalence of sickle cell in three most socio-economically backward group namely schedule cast, schedule tribe and other backward class in India. Prevalence of sickle cell carriers varies from as low as 1% to as high as 40%. Madhya Pradesh is the leading state with highest number of sickle cell heterozygote (more than 9,00,000) and homozygotes (more than 60,000). Out of 45 districts, 25 districts had a high prevalence of Hb S that varies from 10 to 33%. [2]. A recent population survey in Gujarat among more than 1,50,000 tribal population found a prevalence of 11.37% [3]. In eastern state of Odisha with a sizable tribal population, had a sickle cell prevalence of 11 to 12% [4].

Sickle cell disease (SCD) is a group of condition with abnormality in the β-globin gene. It ranges from homozygous condition affecting both gene for β-globin to other genotypes like sickle-cell/β^+ thalassemia (HbS/β^+), heterozygous sickle-cell/β^0 thalassemia (HbS/β^0), sickle-cell/haemoglobin C disease (HbSC), and other less occurring genotypes. In addition to that SCD also shown to have multiple phenotypic variation in addition to genetic variation [5]. Sickle cell anaemia (SCA) is a form of SCD where both genes for β-globin (βs) are mutated and represented by HbSS genotype. It is the severe form of SCD, where the clinical features are more pronounced [6].

Hydroxyurea is one of such drug which induces HbF production and was approved by US-FDA for SCA. It is basically a chemotherapeutic agent used for cancer patient and treatment of HIV. Later on its effect on HbF was discovered [7]. Hydroxyurea provides benefits in patient with SCA through multiple mechanism and can be seen as an ideal drug. Multiple mechanism includes increases HbF production; inhibits HbS polymerization; improves hydration of RBCs; prolongs

life span of RBCs thereby increasing total haemoglobin; changes in RBC rheology; increase in nitric oxide which is a potent vasodilator; and decreases adhesion of RBC to endothelial cells [8]. Hydroxyurea causes myelosuppression by inhibiting an essential enzyme for DNA synthesis i.e., ribonucleotide reductase [9]. Due to this myelosuppression it also causes reduction/normalization of usually elevated white blood cells (WBC) [10].

Hydroxyurea has proven to reduce the morbidity and mortality in SCA patient. Various studies have used different doses of hydroxyurea to prove its clinical efficacy [11]. Moreover maximal tolerated dose (highest dose of drug without any serious adverse event) of hydroxyurea requires continuous monitoring and supervision of clinical and haematological parameters which increases its cost leading to low compliance. In a resource poor setting like India, it is not possible to follow up patients continuously. Two recent studies reported a higher efficacy of low dose hydroxyurea (10 mg/kg/day) in reducing number of blood transfusion and vaso-occlusive crises in patient with SCA. They also reported a less frequent monitoring which increased the compliance and overall survival [12].
Despite of the evidence supporting use of hydroxyurea in SCA are generated in high income countries. There is a paucity of data are regarding use of hydroxyurea in India which is one of the major contributors to the global burden of SCA. Moreover, there is scarcity of evidence from prevalent state like Odisha regarding epidemiological and clinical profile of sickle cell anemia in children. Most of the time the treatment regimen followed with hydroxyurea in children with sickle cell anemia are inadequate and frequently not advised at all.

MATERIALS AND METHODS

The current study was a prospective hospital based observational study was carried out in the Department of Paediatrics, Institute of Medical Sciences and SUM hospital, Bhubaneswar.

All the paediatric population between age group of more than one year to less than 15 years diagnosed with sickle cell anaemia were our study population. A minimum sample of 29 subject was adequate to achieve required power in the study. For the purpose of the study we considered 30 subjects to be included in the study.

Sampling Method: A convenient sampling method was used to select study participants. Since the current study was a hospital based observational study, we approached all the children who were newly diagnosed with sickle cell anaemia to be included in the study. Those subjects who gave consent and ascent to participates were included in the study.

Inclusion Criteria:

a) All newly diagnosed cases of Sickle Cell Anemia coming to Pediatric and Hematology Units.
b) Children between the age of 1 to 15 years.
c) Those whose parents gave consent/ascent to participate in the study.

Exclusion Criteria:

a) Patient diagnosed at other centers and on treatment at our center, but with inadequate clinical details.

b) Co morbidity like renal dysfunction or hepatic impairment
c) HbSAg/HCV/HIV positive cases
d) Those parent and children duo who did not give consent/ascent to participate in the study.

The questionnaire division is as below

i. Section I: Baseline characteristics
ii. Section II: Laboratory investigation before the hydroxyurea therapy
iii. Section III: Laboratory investigation before the hydroxyurea therapy
iv. Section IV: Side-effects of the hydroxyurea therapy

Study Methodology:

A valid consent was taken from the parents (and children where applicable) before enrolling to the study. Hydroxyurea was started at dose of 20mg/kg in the children; and was increased gradually 5mg/kg every eight weeks of therapy to maximum tolerable dose (up to 35mg/kg). Patients were followed up prospectively to document the episodes of vaso-occlusive crisis, transfusion requirement, and specific drug related toxicities. Response to the change in fetal hemoglobin pattern were documented at 3-month, 6-month and at 1 year.

Statistical Analysis and Reporting:

The data collected with were imported to Microsoft Excel 365 and cleaned. The data were further analysed in SPSS version 27 (IBM). All the categorical variable was expressed in term of number and percentages. The association between categorical variable was determined using chi-square test or Fischer exact test. All the quantitative variable was expressed in terms of mean and standard deviation. The normality of the distribution were checked using Shapiro-Wilks test. Independent sample t-test or Mann-Whitney U test was used to compare mean between two groups. Repeated measures ANOVA statistics was used to compare mean within the group for repeated measurements. The categorical data were presented graphically through bar and pie chart whereas the continuous variables were presented using histograms, and box and whisker plots. P value <0.05 will be considered statistically significant.

RESULTS

Table 1: Baseline characteristics of the children

Variables	Mean	Standard deviation	Range
Age (in years)	9.07	2.63	1 – 15
Weight in Kg	19.67	4.29	14 – 30
Height in cm	108.7	7.94	95 – 122

Mean weight of the children at enrollment was 19.67 ± 4.29 kilograms while the mean height was 108.7 ± 7.94 cm. Table 1 describes the baseline characteristics of the study population.

Table 2: Family history of the sickle cell anemia among the study population

Family history	Number	Percentages
Consanguinity		
Present	8	26.7
Absent	22	73.3
Sickling history of father		
Present	30	100
Absent	0	0
Sickling history of mother		
Present	30	100
Absent	0	0

Family history of the sickle cell anemia described in table 2. History of consanguineous marriage was present in 26.7% cases. Sickling history was found in all the parents (100%) including both father and mother.

Table 3: History of symptoms of sickle cell anemia among the study participants

Symptoms	Mean	SD	Range	Proportion having symptoms
Number of Vaso-occlusive crisis	2.67	0.92	1–4	60%
Number of Acute chest syndrome	0.60	0.67	0–2	50%

Number of hospitalizations	1.87	0.68	1–3	76.7%
Number of Blood transfusion	2.80	0.80	1–4	83.3%

At least one vaso-occlusive crisis was seen in 60% of the subject and 50% had acute chest syndrome before hydroxyurea therapy. More than 75% of the subject received blood transfusion while 83.3% admitted to hospital for complications of sickle cell anemia (Table 3).

In the past one year mean number of vaso-occlusive crisis reported was 2.67 ± 0.92 while acute chest syndrome was reported much less i.e., 0.60 ± 0.67. Due to these mean number of hospitalizations reported was 1.87 ± 0.68 and mean number of blood transfusion reported to be 2.80 ± 0.80 (Table 3).

Table 4: Association of weight at different times of follow up

Weight	**Mean**	**Standard deviation**	**F value**	**P value**
Baseline	19.67	4.28	0.830	0.481
First follow up	19.93	4.17		
Second follow up	19.90	4.17		
Third follow up	19.83	4.33		

Mean weight of the participants almost remained constant before therapy and during the follow up with no statistically significant difference (p value = 0.481) (Table 4).

Table 5: Association of hemoglobin level and different hemoglobin types at different times of follow ups

Variables	Baseline	1st follow up	2nd follow up	3rd follow up	F value	P value
Hb	7.27 ± 0.58	7.84 ± 1.00	8.78 ± 0.82	10.02 ± 2.12	32.80	<0.001
HbS	65.51 ± 5.30	65.75 ± 5.45	64.15 ± 5.45	63.06 ± 5.49	47.92	<0.001
HbF	28.00 ± 4.80	28.40 ± 4.84	29.46 ± 4.82	30.56 ± 4.82	133.12	<0.001

Details of the hemoglobin levels are described in table 5.

Table 6: Comparison of different laboratory parameter at different times of follow ups

Variables	Baseline	1stfollow up	2nd follow up	3rd follow up	F value	P value
TWBC	11.383	9601 ± 1168	8763 ± 952	8408 ± 1009	48.54	<0.001

	± 2083					1
Platelet	2.35 ± 0.61	2.07 ± 0.49	2.03 ± 0.51	1.96 ± 0.38	6.83	0.002

Total WBC count was at higher level at the baseline which showed a steady decline during the follow up. This change in mean WBC count was statistically significant with a p value of <0.001. Similarly, platelet count was at higher level at the baseline which showed a steady decline during the follow up. This change in mean platelet count was statistically significant with a p value of 0.002. Details are given in table 6.

Table 7: Comparison of liver parameters at different times of follow ups

Variables	**Baseline**	**1st follow up**	**2nd follow up**	**3rd follow up**	**F value**	**P value**
Total bilirubin	1.69 ± 0.80	1.69 ± 0.47	1.68 ± 0.58	1.58 ± 0.34	0.592	0.572

Direct bilirubin	0.59 ± 0.31	0.55 ± 0.12	0.57 ± 0.14	0.56 ± 0.15	0.270	0.718
SGOT	42.15 ± 22.16	39.17 ± 15.14	40.30 ± 17.58	43.41 ± 16.98	7.946	0.001
SGPT	16.91 ± 8.29	17.17 ± 8.83	16.70 ± 2.83	18.18 ± 5.09	8.813	<0.001

Total bilirubin and direct bilirubin did not show any statistically significant difference in their change in mean values at different times of follow up (P value >0.05). Liver enzyme like SGOT and SGPT showed a rise from baseline to the end of the third follow up. This difference was statistically significant with p value >0.001. The details of the liver parameters are given in table 7.

Number of complications before therapy was compared to number of complications after therapy (during the follow up period) and shown in table 8. Mean number of vaso-occlusive crisis experience by subjects before therapy was 2.67 ± 0.92 compared to 0.27 ± 0.45 which was highly statistically significant (P value <0.001). Similarly, number of acute chest syndrome, number of blood transfusion and number of hospitalizations showed a statistically
significant decline during the follow up period compared to the baseline with a p value <0.05. Details are given in table 8.

Table 8: Comparison of complications before and after the hydroxyurea therapy

Complications	Before therapy (Mean ± SD)	During follow up (Mean ± SD)	t-value	P value
No. of VOC	2.67 ± 0.92	0.27 ± 0.45	13.10	<0.001
No. of ACS	0.60 ± 0.67	0.13 ± 0.34	3.29	0.003
No. of Blood transfusion	2.80 ± 0.80	0.67 ± 0.71	9.77	<0.001
No. of hospitalization	1.87 ± 0.68	0.27 ± 0.45	12.10	<0.001

Table 9: Comparison of proportion of complication before and after the therapy

Complications	Before therapy N (%)	During follow up N (%)	P value
VOC			
Present	18 (60.0)	9 (30.0)	0.035
Absent	12 (40.0)	21 (70.0)	
ACS			
Present	15 (50.0)	4 (13.3)	0.007
Absent	15 (50.0)	26 (86.7)	
Blood transfusion			
Present	23 (76.7)	16 (53.3)	0.042
Absent	7 (23.3)	14 (46.7)	

Hospitalization Present Absent			
	25 (83.3)	8 (26.7)	<0.001
	5 (16.7)	22 (73.3)	

We also compared the proportion of subject experience specific complications before and after the therapy and compared them (Table 9). The proportion of subject experience symptom of vaso-occlusion was 60% before therapy which declined to 30% after therapy. This difference in proportion was statistically significant (P value = 0.035). Similarly, we found a significant decrease in proportion of subject with acute chest syndrome, blood transfusion and hospitalization with a p value of <0.05.

Table 10: Side effects of the hydroxyurea therapy

Side effects	**Number**	**Percentages**
Gastrointestinal problem	8	26.67
Rash	5	16.7
Skin tanning/pigmentation	2	6.67

Table 10 shows the side effect profile of the hydroxyurea. Most common side effect was gastrointestinal problem followed by rash (16.7%). Only few subject showed skin pigmentation (6.67%).

Table 11: Beneficial effect of hydroxyurea therapy

Organomegaly	***Before therapy*** *N (%)*	***After therapy*** *N (%)*	***P value***
Appetite Good Poor			
	14 (46.7)	20 (66.7)	0.034
	16 (53.3)	10 (33.3)	

General wellbeing			
Good Poor	12 (40.0)	16 (53.3)	0.072
	18 (60.0)	14 (46.7)	
Pain score	5.57 ± 1.54	4.27 ± 1.14	0.001

Appetite among the children was improved from 46.7% before therapy to 66.7% after hydroxyurea therapy. This change in proportion was statistically significant (P value = 0.034). General wellbeing among the children showed a non-significant improvement from 40% to 53.3%. We also determined pain using a 10-point likert scale. The mean pain score before therapy was 5.57 ± 1.54 compared to a lesser pain score of 4.27 ± 1.14 during the follow up. This difference in mean was statistically significant (p value = 0.001). Details were given in table 11.

DISCUSSION

Painful crisis due to sickle cell anemia is considered as a significant morbidity and any therapy or intervention which reduces these complications can be a worthwhile investment. Moreover reduction in complication and hospitalization has an positive impact on the health, wellbeing, and quality of life of the patient/children. Indirectly it helps in reducing out of pocket expenditure and ultimately reducing financial burden. Our study suggested that hydroxyurea is one such therapy which can reduce the complication or painful crisis in patient suffering from sickle cell anemia which was supported by other studies [13].

An open label clinical trial by Charache et al. reported a significant improvement in median time to first and second crisis from 4.6 months to 8.8 months (P value = 0.01). They also reported a significant reduction in acute chest syndrome (from 51 to 25 episodes) and significant reduction in blood transfusion (from 73 to 48 blood transfusion) in enrolled patients without any significant adverse effect in patients due to hydroxyurea therapy [14].

In a multicentric phase 3 clinical trial of hydroxyurea among 193 pediatric sickle cell patients found a significant reduction of recurrent episode of painful crisis, dactylitis, hospitalization and chest syndrome. They also reported a lower rate of blood transfusion among the patients. Despite of the inherent property of myelosuppression, hydroxyurea did not cause any rise in serious infection [15].

A two year follow up clinical trial suggested that the major adverse effect was transient neutropenia resulting in viral like illness. They reported an increased level of hemoglobin level and HbF percentages in the patient receiving hydroxyurea therapy which was statistically significant. The study also showed a higher percentage of functional spleen in patient receiving hydroxyurea therapy [16].

The current study showed a reduction in leucocyte and platelet counts after hydroxyurea treatment compared to the baseline. These findings is supported by previous research on children [17]. The

reduced leucocyte count and platelet is considered as beneficial in these patients as higher level of them triggers vaso-occlusive crisis [18]. Decrease in the level of these circulatory inflammatory biomarker decrease the vaso- occlusive crisis in sickle cell anaemia patients [19]. Although reduction of leucocyte and platelet are good sign but higher reduction may lead to higher probability of infection/bacteraemia and bleeding episodes respectively. Therefore, it is advisable to have a continuous monitoring of cell counts to mitigate the complications.

Our study demonstrated a significant increase in the foetal haemoglobin level after 12 months of follow up compared to the baseline. The main mechanism of action of hydroxyurea in patients with sickle cell anaemia is the induction foetal haemoglobin production which alters the pathogenesis [20]. Higher level foetal haemoglobin prevents the sickling of red blood cell in patients with sickle cell anaemia and thereby reducing the complications. Higher foetal haemoglobin level has also shown to reduce disease severity [21].

The current study has also showed a higher safety profile of hydroxyurea in the study population. Many of the children in our study reported an improved appetite and higher level of energy. The biological reason for this may be lies in the increase in red cell parameters increased by hydroxyurea therapy. The enhanced red cell level increases the oxygen carrying capacity thereby improving the day to day activities among the children.

Only a few patients in our study complained of vomiting, pain abdomen, diarrhoea and other gastrointestinal symptoms. During the follow ups we noticed that these symptoms are transient and cured with time. As a chemotherapeutic agent, hydroxyurea has known gastrointestinal side-effects but these are not severe to discontinue the treatment. Only one patient in our study reported hyperpigmentation of skin, which was also a known side-effect of hydroxyurea [22].

CONCLUSION

Hydroxyurea therapy is an effective mode of treatment for children with sickle cell anemia. Hydroxyurea is one such therapy which can reduce the complication or painful crisis in patient suffering from sickle cell anemia and also Hydroxyurea reduces number of hospitalizations, and blood transfusions. Using Hydroxyurea in children suffering from with sickle cell anemia cause raise in Hemoglobin levels, with decrease in HbS and increase in HbF level significantly. Hydroxyurea therapy can cause reduced platelet, neutrophil counts and liver enzymes derangement, but these are not severe and complications like cytopenia are very rarely seen. Hydroxyurea improves quality of life in children suffering from sickle cell anemia.

Although Hydroxyurea shown to have a positive effect on children suffering from sickle cell anaemia, but caution should be taken before universalizing its use. Genetic variability of sickle cell disease, geographic variability, patient characteristics, health facility, resources to handle complications are the few constraints to be addressed before initiating hydroxyurea therapy. Side effect profile of the hydroxyurea is less studied and most of the literature focussed on the short-term side-effect/adverse effect of hydroxyurea. So, further robust researches should be carried out to find out long term adverse effect of the hydroxyurea.

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