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CLINICAL AND HEMATOLOGICAL EFFECTS OF HYDROXYUREA THERAPY IN MANAGEMENT OF SICKLE CELL ANEMIA

Dr. Manisha Panda,¹ Dr. Venkat Lakshmi Gondu^{2*}

¹Assistant Professor, Department of Community Medicine, JIS School of Medical Science & Research, Kolkata, West Bengal

^{2*}Assistant Professor, Department of Community Medicine, Shri Rawatpura Sarkar Institute of Medical Sciences and Research, Raipur, Chhattisgarh

Corresponding Address

Email: dr.lakshmigv@gmail.com

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ABSTRACT

Background: The most predominant form of haemoglobinopathy worldwide is sickle cell disease. The greatest burden of the disease lies in sub-Saharan Africa and Asia⁵.

Objective: To evaluate the effectiveness of HU therapy in sickle cell disease as measured by decrease in crises rate, hospital admissions, days of hospitalization and number of blood transfusions.

Methods: the study was conducted on 79 children of 1-16 year age. Out of which in only 75 patients Hydroxyurea therapy was started as they were found to be eligible. 16% of the patients responded to 15 mg/kg/ day of HU, 50.66% responded to 20 mg/kg/ day, 29.33% to 25 mg/kg/ day and only 4% needed a dose escalation to 30 mg/kg/ day for the response.

Results: Our study showed a significant reduction in the VOC rate from 243 episodes to 46 episodes (p value <0.001), the number of ACS reduced from 37 episodes to 5 episodes (p value <0.001), also there is a significant decline in the rates of hemolytic crises from 63 episodes to 10 episodes per year, Significant increase in the HbF levels from 15.87±5.50% to 21.77±4.06% (p value <0.001). There was a definite and significant reduction in the number of hospitalization days from 7.76±4.76 to 3.79±2.29 days and in the number of admissions per year dropped significantly from 4.80 ± 1.41 to 1.42± 0.61 per year.

Conclusion: Hydroxyurea reduced the frequency of painful crises and diminished the number of hospitalization, transfusion, and episodes of acute chest syndrome¹⁷.

Keywords: Haemoglobin (Hb), Hydroxyurea (HU), Mean Corpuscular Volume (MCV), Platelet Counts, Sickle Cell Disease (SCD), White Blood Cells (WBC).

INTRODUCTION

The most predominant form of hemoglobinopathy worldwide is sickle cell disease. The greatest burden of the disease lies in sub-Saharan Africa and Asia. Sickle cell disease in Indian population has a variable though relatively mild clinical presentation compared to Africans.¹ Many patients particularly among the tribal groups from Orissa in the east, the Nilgiris in the south, and Gujarat in the west have an unusually mild disease course similar to that described earlier in the eastern province of Saudi Arabia. This has been attributed to the very high frequencies of α -thalassemia and high fetal hemoglobin levels seen in these cases.²

Hydroxyurea was shown to induce fetal hemoglobin (HbF) synthesis, which influences the clinical severity of sickle cell anemia, leading to milder symptoms and longer survival in patients with higher HbF levels. However, it has been reported that hydroxyurea has mixed effects on erythroid precursors, depending on genotypic variation and all patients do not respond equally well to hydroxyurea.³

In most US studies of HU therapy for patients with SCA, the HU dose has been increased to maximum tolerated dose (MTD), typically defined as a maximum of 30-35 mg/kg/day. In contrast, European reports describe HU response at lower doses of 20-25 mg/kg/day, with no attempt to achieve MTD.⁴

This study was conducted to evaluate the effectiveness of HU therapy in sickle cell disease as measured by decrease in crises rate, hospital admissions, days of hospitalization and number of blood transfusions. This also evaluated the hematological response in terms of increased fetal hemoglobin, hemoglobin concentration, MCV and decreased WBC and platelet counts. This also depicted the adverse reactions of short-term HU therapy.

MATERIAL AND METHODS

In the present study we assessed the clinical and hematological effects of Hydroxyurea therapy in sickle cell disease patients aged 1-16 years at Department of Community Medicine, Shri Rawatpura Sarkar Institute of Medical Sciences and Research, Raipur, Chhattisgarh. We have examined 79 patients out of which in only 75 patients Hydroxyurea therapy was started as they were found to be eligible.

Any patient with frequent VOC which has 3 or more hospitalizations for VOCs involving the extremities or trunk, or 1 or more hospitalizations for VOCs of lungs (acute chest syndrome) in the preceding 12 months, Severe anemia, 1 or more episode of cerebrovascular attack or sequestration crises or aplastic crises were included in the study.

Patients who had high Serum creatinine level, serum alanine aminotransferase (ALT) level, Failure to comply with schedule medication and follow up, Medications that could potentially enhance HU toxicity, Pregnancy and Human immunodeficiency virus infection were excluded from the study.

For all the statistical analysis computer software was used. The information collected was tabulated and the data was analyzed using suitable statistics. Mean, Standard deviation, Percentage, Frequency, and "paired t test" test was used.

RESULT

Our study showed a significant reduction in the VOC rate from 243 episodes to 46 episodes (p value <0.001) after hydroxyurea therapy. In our study, the number of ACS reduced from 37 episodes to 5 episodes (p value <0.001) after hydroxyurea therapy. In our study, there is a significant decline in the rates of hemolytic crises from 63 episodes to 10 episodes per year which is statistically significant. HU has a beneficial effect on the hemolytic crises. Most of the researchers have not shown a reduction in the hemolytic crises in their study.

Our study showed a significant reduction in the number of transfusions reduced significantly from 8.10 ± 5.50 /year to 3.98 ± 4.06 per year. There was a definite and significant reduction in the number of hospitalization days from 7.76 ± 4.76 to 3.79 ± 2.29 days and in the number of admissions per year dropped significantly from 4.80 ± 1.41 to 1.42 ± 0.61 per year.

It is well established fact that HU causes increased levels of HbF which contributes to the most beneficial effects of HU therapy. So, is the same in our study which showed a significant increase in the HbF levels from $15.87 \pm 5.50\%$ to $21.77 \pm 4.06\%$ (p value <0.001).

It is proven that reduction in the WBC counts has a beneficial effect on the pathogenesis of VOC. After HU therapy, we got a significant reduction in ANC and significant reduction in WBC counts from 7.1 ± 1.32 to $4.81 \pm 1.12 \times 10^9/l$ and from 13.43 ± 4.65 to $7.53 \pm 2.89 \times 10^9/l$ respectively, which shows the indirect effect of HU therapy on the reduction in the rate of VOC.

By HU therapy, the mean MCV raised significantly from 80.37 ± 10.35 to 105.6 ± 17.34 fl. After HU therapy, the hemoglobin raised significantly from 6.29 ± 1.70 gm/dl to 9.72 ± 1.59 gm/dl. There was a significant reduction in the reticulocyte percentage from $2.28 \pm 1.31\%$ to $1.14 \pm 0.86\%$ which shows indirectly the effect of HU on the reduction in the hemolysis.

The effect on the VOC is contributed by the reduction in the platelet counts which in our study was significant from 4.25 ± 0.78 to $2.96 \pm 0.76 \times 10^9/l$. The toxicities reported in the present study were mostly due to myelosuppression and all of them were reversible requiring rarely any dose modification. This was probably due to the reason that we didn't escalate the dose to MTD in the present study. Most of the adverse effects required only temporary discontinuation of therapy out

of which headache and nausea were the most common ones. Only 4 patients were excluded from the present study, 3 from avascular necrosis and 1 due to death. The lesser dropout rate is due to better compliance in our study.

DISCUSSION

In our study, 34.7% cases were in the age group 0-5 years, 46.7% of cases were in 5-10 years, 18.7% were in 10-15 years. The youngest case is a 1 year 4 months old male. The mean age of patients in our study was 7.2 years and median age was 7 years which was similar to that of Jayabose et al and Eggleston et al.

In our study, 16% of the patients responded to 15 mg/kg/ day of HU, 50.66% responded to 20 mg/kg/ day, 29.33% to 25 mg/kg/ day and only 4% needed a dose escalation to 30 mg/kg/ day for the response. The mean average dose in our study was 21 mg/kg/day. We have got a better response than Parvine et al as in their study only 41% of the patients responded to a dose of up to 20mg/kg/ day as compared to 66% in our study. The present study is similar to Scott et al.

In our study, the maximum dose of Hydroxyurea was 30 mg/kg and is similar to that taken by other researchers like Parvine et al, Kinney et al, and Eggleston et al. The higher maximum dose in the study by Zimmerman et al and Jayabose et al can be explained by their study design which is supposed to assess the response and toxicities at maximum tolerated dose of HU. Kinney et al took a fixed dose of HU from the starting till end of the therapy as it was as per their study protocol.

In our study, the number of VOCs reduced significantly from 243 episodes to 46 episodes (p value <0.001) after hydroxyurea therapy. Jayabose et al, Singh H et al, Parvin et al, Charache and Terrin et al, reported a similar reduction in the VOCs which was statistically significant. Scott et al, Zimmerman et al, Eggleston et al didn't make a comment on the VOC status.

In the present study, the number of admissions per year dropped significantly from 4.80 ± 1.41 to 1.42 ± 0.61 per year. Our study result is similar to that of Harminder Singh et al, Parvine et al reported a statistically significant reduction in the number of admissions from $(2.76 \pm 2.3/\text{yr})$ to $1.15 \pm 1.9/\text{yr})$ which was less than in our study, as the duration of the study was 5 years which might have led to decrease in response with time. In study by Scott et al, the number of admissions per year decreased insignificantly from, $7 \pm 2.4/\text{year}$ to $3.0 \pm 4.0/\text{year}$. The dissimilarity from our study and the better result is due to the fact that the number of patients (n= 10) analyzed were less similar to Charache & Terrin et al and in contrast with Jayabose et al, Charache & Terrin et al, didn't make a comment on the number of admissions per year.

In our study, we found a significant rise in HbF from a pretreatment level of $15.87 \pm 5.50\%$ to $21.77 \pm 4.06\%$ (p value <0.001). Our study correlated with that of Singh et al in relation to HbF parameter, they reported an increase in HbF% from 12.83% to 19.17%. In the study by Scott et al also reported a significant rise in HbF from a value of $6.9\% \pm 6.0\%$ to $15.2\% \pm 9.8\%$, but the final HbF level was lower than in our study which may be due to the selection of older age group of patients from 10- 17 years in contrast to our study where age group of patients ranged from 1-16 year. Kinney et al, reported a significant fall in % HbF from 21.8 ± 7.8 to $20.3 \pm 4.9\%$ which is different from our study, the reason for the difference being the higher physiological levels of HbF % in this age group (6-28 months). The maintenance of relatively stable % HbF in these patients demonstrate a clear response to Hydroxyurea when compared with the expected declines in those levels. reported a significant rise in % HbF concentration from $4.65 \pm 4.61\%$ to $15.34 \pm 11.3\%$ but was less than that of our study as their study duration was of 6 months. Charache & Terrin et al has also reported a rise in % HbF but the data is insufficient for comparison with our study. Kinney et al didn't make a comment on the rise in % HbF level.

% HbF is a strong predictor of hospitalizations and transfusions in children with sickle cell anemia. The higher % HbF are associated with decreased number of hospitalizations and transfusions. Beneficial effect of HU is well established on both hematologic values and clinical symptoms is due to the induction of fetal hemoglobin synthesis as the extent of polymer formation is inversely proportional to the concentration of HbF. In the present study, we found a statistically significant increase in the hemoglobin concentration from 6.29 ± 1.70 gm/dl to 9.72 ± 1.59 gm/dl. No patient in our study sustained a consistent fall in Hb concentration. Scott et al¹⁷ and Jayabose et al both found a significant increase in the Hb level and were similar to the present study. Harminder et al and Parvine et al reported a lesser increase in hemoglobin level from 9.15 to 9.98gm/dl and 8.2 ± 1.1 to 8.8 ± 1.2 gm/dl respectively. The difference from our study can be explained from the maximum dose of HU (30mg/kg) in our patients which is more than in their study where majority of the patients were treated with a dose ranging from 20-25mg/kg. Kinney et al, reported a non significant increase in the hemoglobin level from a value of 8.4 ± 1.7 gm/dl to 8.7 ± 1.0 gm/dl and 8.1 ± 0.75 to 8.5 ± 0.83 gm/dl respectively. The reasons for this lesser rise may be the lesser duration of their study, 3 months and 6 months respectively, as compared to the present study. Charache & Terrin et al has reported an increase in the Hb concentration but the data is inconclusive for comparison with our study. Kinney et al,¹⁸ didn't make a comment on the rise in the Hemoglobin concentration. After Hydroxyurea therapy, the overall blood flow is improved, with a higher hemoglobin concentration and lower LDH and bilirubin levels. Concerns

about the deleterious effects related to a higher hemoglobin concentration causing higher blood viscosity do not appear clinically relevant, presumably because of counteracting benefits from increased cellular hydration and deformability, decreased adhesiveness, and overall improved rheology.

A remarkable attribute of Hydroxyurea is the observation beyond HbF induction, the cytotoxic effects of Hydroxyurea also reduce marrow production of neutrophils and reticulocytes, because an elevated WBC has been associated with both morbidity and mortality of SCA, lowering the WBC count in SCA is potentially therapeutic. Both neutrophils and reticulocytes promote vaso-occlusion through vascular adhesion; hydroxyurea lowers their absolute numbers and reduces surface expression of adhesion receptors. An elevated WBC count by releasing pro-inflammatory cytokines has been implicated as a risk factor for a number of vaso-occlusive complications, and the suppression of neutrophil formation may partially explain the clinical benefits of Hydroxyurea. Miller et al in their study on a cohort of 392 infants suffering from SCA Concluded that three easily identifiable manifestations of sickle cell disease that may appear in first two years of life (leukocytosis, dactylitis and severe anemia) help to predict the possibility of severe sickle cell disease later in life.

In our study, we found a statistically significant reduction in (ANC) absolute neutrophil count ($10^9/l$) from 7.1 ± 1.32 to 4.81 ± 1.12 . Our study is similar to the study by Jayabose et al. Kinney et al and Zimmerman et al reported a greater reduction in ANC from 7.0 ± 3.0 to 4.4 ± 2.2 and 6.2 ± 2.9 to 3.5 ± 1.9 respectively. Their better results can be attributed to their protocols in which the patients were treated at maximum tolerated dose (MTD). Kinney et al also found a greater fall in value from 7.43 ± 1.6 to 4.6 ± 1.76 as compared to our study. Parvine et al²⁵ also noted a statistically significant decrease in the ANC which was better as compared to our study the reasons for which might have been the broad age range of patients in their study and due to the better immunity acquired with age their infection rates might have been lower leading to better results. Eggleston et al, Charache & Dover et al, Charache & Terrin et al, Scott et al, Maeir et al, Harminder et al has not made a comment on the reduction of ANC in their study. An elevated WBC count has been implicated as a risk factor for a number of vaso-occlusive complications of SCA and suppression of neutrophil formation may partially explain the clinical benefits of hydroxyurea.

In our study the platelet counts ($10^9/l$) reduced from 4.25 ± 0.78 to 2.96 ± 0.76 which was a significant reduction. Our study is similar to the study by Jayabose et al, reported a greater reduction in platelet from 4.21 ± 0.99 to 3.38 ± 1.17 . Zimmerman et al and Kinney et al reported a greater decline in the platelet counts from 4.86 ± 1.92 to 3.79 ± 1.61 and from 4.61 ± 1.57 to 3.71 ± 1.53 respectively, the reason for this was the study protocol which used the MTD of HU to look for effects in both of these studies. Hankins et al reported a significant decline from 4.10 ± 1.69 to 3.73 ± 2.38 but was lesser reduction than in our study the reason for which is the longer duration of their study, 4.9 ± 1.3 years, as compared to ours which must have caused a decreased marrow response with time.

In our study, MCV rose in large number of our treated subjects, and in those patients who did not have greater increases in MCV were those who were not HbSS but HbS- β -thalassemia patients. Hydroxyurea as an antimetabolite is well known to induce macrocytosis. The mean MCV rose significantly from 80.37 ± 10.35 to 105.6 ± 17.34 fl. The constant presence of macrocytosis in our patients and in those in other studies who responded to hydroxyurea by increasing fetal hemoglobin synthesis may indicate that factors controlling F cell production may interact directly or indirectly with the determinants of erythrocyte volume regulation.

In our study, reticulocyte counts decreased significantly from a pretreatment value of $2.28 \pm 1.31\%$ to $1.14 \pm 0.86\%$ which point towards reduced hemolysis. To explain the paradoxical rise in Hb concentration in patients receiving the myelotoxic agent HU, we examined their reticulocyte response. Zimmerman et al, and Kinney et al found a similar statistically significant decrease in reticulocytes. The greater reduction in the study by Kinney et al, may be due to the lesser number of patients in the study and the higher initial values. The lesser decrease in the reticulocyte percentage in the study by Kinney et al, and Jayabose et al also may be due to the lesser number of patients being evaluated in their study i.e. 21 and 15 respectively. Charache & Terrin et al has also reported a decrease in the reticulocyte count but the data is insufficient for comparison with our study. Harminder Singh et al, Parvine et al didn't make a comment on the reticulocyte count change.

In our study, headache was the most frequent complaint, reported by 17 patients taking the therapy. Most of these patients returned to the study after proper counseling. The nausea reported by the 13 patients decreased on taking the drug during the bedtime. No patient had gastrointestinal complaint severe enough to warrant permanent stoppage of HU treatment. One patient stopped taking her HU therapy at 7 months when she acquired a rash for which she did not seek medical attention and therefore the cause of rash could not be ascertained. She subsequently returned to the therapy after 2 weeks of discontinuation. Drowsiness was reported in 7 patients, mild alopecia in 1, melanonychia in 1 patient and leg ulcer in other patient and diarrhea in 3x patients. Dermatologic side effects of Hydroxyurea are fairly common and include hyperpigmentation, scaling erythema and desquamation of the face and hands, and partial alopecia. Hydroxyurea induces

painful leg ulcers that are usually difficult to treat and require cessation of HU therapy. 1 patient in our study developed leg ulcer although an Occurrence of 8.5% is found in patients on continuous HU for chronic myelogenous leukemia or other myeloproliferative disorders. Other common side effects reported by other researchers included gallstones, papillary necrosis, bleeding, TIA, Priapism, pregnancy, ALL, secondary amenorrhoea, herpes zoster, and megaloblastic anemia.

CONCLUSION

Our study showed a significant reduction in the VOC rate, the number of ACS, also there was a significant decline in the rates of hemolytic crises, Significant increase in the HbF levels, There was a definite and significant reduction in the number of hospitalization days and in the number of admissions per year dropped significantly.

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Table 1: Age and gender distribution of study population

AGE GROUP (yrs)	NUMBER OF		Total
	Male	Female	
0 – 5	14	12	26
6 – 10	21	14	35
11 - 15	5	9	14
Total	40	35	75

Table 2: Types of crises

	Frequency	Percentage
VOC	286	79.44
ACS	3	0.83
Aplastic crises	2	0.55
Hemolytic crises	60	16.66
Sequestration crises	9	2.5
Total	360	100

Table 3: Caste distribution of the study population

Caste	Frequency
Sahu	14
Other Backward Castes (Dheewar,Hitwar,Kalaar,Sinha,Nishad,Manikpuri,Naik,Chandra)	11
Scheduled Castes (Uikey, Mehar, Ghasia, Mighea, Satnami, Nai)	10
Ganda	7
Scheduled Tribes (Gowari, Halba, Kewat, Sidar)	4
Teli	4
Kurmi	3
Verma	3
Yadav	2
Muslim	2
Patel	2
Baghel	1
Bairagi	1
Brahman	1
Dhruv	1
Chauhan	1
Chaudhary	1
Christian	1
Rajput	1
Oriya	1
Pinjara	1
Ghasi	1
Gonda	1
Agarwal	1

Table 4: pre and post hematological variables

		Mean	Std. Dev	P value
VOC	Before	3.85	1.56	<0.001**
	After	0.85	0.43	
Number of transfusion (Ntranf)	Before	8.10	5.50	<0.001**
	After	3.98	4.06	
HbF	Before	15.87	5.50	<0.001**
	After	21.77	4.06	
Hb	Before	6.29	1.70	<0.001**
	After	9.72	1.59	
WBC count	Before	13.43	4.65	<0.001**
	After	7.53	2.89	

Absolute neutrophil count (ANC)	Before	7.10	1.32	<0.001**
	After	4.81	1.12	
Platelet count	Before	4.25	0.78	<0.001**
	After	2.96	0.76	
MCV reading	Before	80.37	10.35	<0.001**
	After	105.64	17.34	
Reticulocyte count	Before	2.28	1.31	<0.001**
	After	1.14	0.86	

Table 5: Frequency of adverse events

Events	Number of patients
No adverse event	31
Headache	17
Nausea	13
Drowsiness	7
Diarrhoea	3
Alopecia	1
Leg ulcer	1
Melanonychia	1
Rash	1