



## Effectiveness of Hydroxyurea Therapy in Sickle Cell Disease and Sickle Cell Trait

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### Abstract

**Background and Objectives:** Vaso-occlusive crisis, a common clinical presentation of sickle cell disease is a major cause of morbidity. It has been observed in some cases of sickle cell trait also. Hydroxyurea exerts beneficial effect primarily by increasing fetal hemoglobin and also through other mechanisms. The Arabian-Indian haplotype of Hemoglobin S is associated with moderate form of disease and high fetal hemoglobin level. This study was conducted to assess the clinical and hematological response of homozygous and heterozygous cases of Hemoglobin S to hydroxyurea therapy. The adverse reactions to the drug were also observed.

**Material and Methods:** The study, an interventional case series, was conducted at a teaching hospital in Central India during January 2013 to December 2014. A total of 54 cases satisfying eligibility criteria were recruited. 9 cases (2 due to severe reaction and 7 due to poor compliance) were excluded. Thus study comprised of 45 cases of sickle cell disease (36 homozygous and 9 heterozygous). Detailed clinical examination, baseline investigations and HPLC were performed. Cases received 10 mg/kg/ day of Hydroxyurea and were followed up weekly in sickle-cell opd for compliance, effectiveness and adverse reactions. At the end of one year of hydroxyurea therapy, baseline investigations and HPLC were repeated. Appropriate statistical analysis was done using STATA version 13.1.

**Results:** Statistically significant clinical response, namely decrease in the frequency of vaso-occlusive crises and duration of hospitalization and improvement of clinical score was observed ( $p < 0.0001$ ) in homozygous and heterozygous cases of sickle cell disease. Statistically significant hematological response ( $p < 0.0001$ ) namely, increase in hemoglobin, mean corpuscular volume of red cell and fetal hemoglobin level, decrease in total leukocyte count was observed in homozygous and heterozygous cases of sickle cell disease. Hydroxyurea was well tolerated.

**Conclusion:** Hydroxyurea is effective in homozygous cases of sickle cell disease. Hydroxyurea is effective in HPLC proven heterozygous cases of sickle cell; however, detailed hemoglobin structure and genetic studies recruiting larger number of these cases is recommended. Hydroxyurea is effective despite high level of fetal hemoglobin. Hydroxyurea is well tolerated and must be administered with regular monitoring.

**Keywords:** Sickle cell disease (SS), sickle cell trait (AS), hydroxyurea, fetal hemoglobin, clinical response, hematological response, adverse reactions.

### Introduction

Sickle cell anemia, a heritable hematologic disease, has various clinical presentations; anemia, vaso-occlusive crisis, aplastic crisis, crippling

avascular bone necrosis and osteomyelitis to name a few. It can manifest in infancy or may remain asymptomatic till adulthood. Clinical presentation varies according to region and patients. This

phenotypic heterogeneity despite mutational unicity led to the identification of five haplotypes of beta-globin gene-Benin, Senegal, Bantu, Cameroon and Arabian-Indian. Arabian Indian haplotype, prevalent in India, is associated with moderate form of disease.<sup>1</sup>

Our hospital is a tertiary care centre which caters to Sickle Cell patients throughout the year. Severe vaso-occlusive crisis similar to homozygous state have been consistently observed over the years in some cases of sickle cell trait also; however, there is limited published literature.<sup>2</sup> Higher level of Fetal hemoglobin (Hb F) is associated with reduction in the frequency and severity of vaso-occlusive crisis.<sup>3</sup> Hydroxyurea, a myelo suppressive agent increases the HbF level. Usefulness of hydroxyurea in sickle cell disease has been demonstrated in Multicentre Study of Hydroxyurea (MSH)<sup>4</sup>. Hydroxyurea has been found to be effective in heterozygous conditions like hemoglobin SD- Punjab and hemoglobin SC<sup>5,6</sup>. Arabian-Indian haplotype is associated with higher HbF level.<sup>7</sup> Hence it may be argued that hydroxyurea may not be beneficial; however hemorheologic actions of hydroxyurea also contribute to its role in management of vaso-occlusive crises. Therefore we have attempted to evaluate the effectiveness of hydroxyurea in homozygous and heterozygous sickle cell patients in vaso-occlusive crisis and correlate the response with baseline fetal hemoglobin level.

### Aims and Objectives

1. To assess the clinical response to hydroxyurea therapy by comparing the frequency of vaso-occlusive crisis during the preceding year, with frequency during one year, of hydroxyurea therapy in sickle cell patients.
2. To assess the hematological response to hydroxyurea therapy by comparing fetal hemoglobin and Hemogram at baseline and at the end of one year of hydroxyurea therapy in sickle cell patients.

3. To compare the clinical {i.e. frequency of acute crisis} and hematological {i.e. HbF levels and Hemogram} response to hydroxyurea drug therapy between *sickle cell disease* and *sickle cell trait patients*.
4. To study Adverse Drug Reactions to the hydroxyurea therapy.

### Material and Methods

This Interventional, non-randomized prospective case series was conducted with the permission of The Institutional Ethics committee. The cases of sickle cell disease (SS) and trait (AS), fulfilling all eligibility criteria, attending general medicine, sickle cell OPD and medicine wards were included after obtaining written informed consent. Sickle cell disease (SS) and sickle cell trait (AS) patients, age > 12 yrs with >3 painful vaso-occlusive crises per year were included. Following cases were excluded-a) Patients with pancytopenia Platelet count less than 100,000/cu.mm, Neutrophil count less than 2,500/cu.mm and Haemoglobin less than 6 g/dl (in accordance with MSH)<sup>4</sup> b) Patients who have received blood transfusion within 3 months at recruitment or who will receive blood transfusion in last 3 months of intervention to eliminate erroneous estimation of HbF levels c) Noncompliant cases d) pregnant women e) cases who develop adverse reactions to the drug.

### Definitions

1. **Vaso-occlusive crisis (VOC):** A painful crisis was defined as a visit to a medical facility that lasted more than four hours, for acute sickling-related pain, which was treated with a parenterally administered narcotic. The episode of pain in the extremities, back, abdomen, chest or head that lasted for some hours could not be explained except by sickle cell state.<sup>4</sup> Only those crises which led to medical visit and admission to emergency department or indoor wards were included. The painful crises managed at home with hydration and oral analgesics were excluded. All our cases had

the documentary evidence of having received parenteral tramadol.

**2. Compliance with the drug hydroxyurea:** compliance was checked by pill count. Patients with more than 90% compliance with the drug were included.

After recruiting sickle cell patients (both SS and AS pattern) as per above eligibility criteria a detailed history and complete clinical examination was performed. Clinical score was calculated (.see table) Complete blood count was done and diagnosis of sickle cell disease and trait was confirmed by High Performance Liquid Chromatography (HPLC) method.<sup>8</sup> Then patients were started on hydroxyurea drug 10 mg/kg/day.<sup>4</sup> Patients were regularly followed up every week in the sickle cell clinic for one year; regular complete blood count monitoring and pill count was done. HPLC and complete blood count were done again at the end of one year.

**Statistical analysis:** continuous variables (age, hemoglobin, fetal hemoglobin, mean corpuscular

volume, platelet count, total leukocyte count) are presented as Mean ± SD. Median and Range were calculated for non-normalized data. Categorical variables (sex, pattern, vaso-occlusive crisis, hospitalizations due to severe vaso-occlusive crisis, blood transfusions and clinical score) are expressed as actual numbers and percentages. Continuous variables were compared at baseline and after one year of hydroxyurea therapy by performing paired –t test for normalized data and Wilcoxon Sign-rank test was applied for non normalized data. Change in hemoglobin during hydroxyurea therapy was assessed by ANOVA test.

The correlation of clinical and hematological parameters with baseline fetal hemoglobin levels was assessed by calculating Pearsons correlation coefficient.

The p-value <0.05 was considered as statistically significant. Statistical software STATA version 13.1 was used for statistical analysis.

Scoring system for clinical evaluation of patients<sup>9</sup>

SCORE→	1	2	3	4	5
Vaso-occlusive crisis in preceding year	0 to 1	>1 -3	>3-5	>5-8	>8-12
Hospitalizations due to vaso-occlusive crises in last 1 year	0	1-2	3-4	≥5	
Blood transfusions in last 1 year	0	1-2	3-4	≥5	
Acute chest syndrome	No	Yes			
Stroke	No	Yes			
Avascular necrosis of femur	No	Yes			
Spleen size	Not/just palpable	3-4cm	5-7cm		

**Observations and Results**

**Table 1.** Clinical parameters before and after starting hydroxyurea

CLINICAL PARAMETERS	one year before starting hydroxyurea (N=45) Mean(± SD) (Range)	During one year of therapy (N=45) Mean(± SD) (Range)	p-value
Frequency of VOC	10.47(±6.59) 3 - 25	1.93(±3.09) 0- 12	<0.0001
Patients requiring hospitalization due to VOCs	38	15	<0.0001
Duration of hospitalization (days)	6.06(± 2.41)	3.76(± 1.37)	0.0011
Frequency of hospitalizations due to VOCs	2.04(±1.30) 0-6	0.44(± 0.72) 0-3	<0.0001
number of blood transfusions	0.31 (±0.73) 0-4	0.02 (± 0.15) 0-1	2.725
clinical score	11.75(±1.71) 9-17	8.29(±1.73) 6-14	<0.0001

**Table 2** Hematological parameters before and after starting hydroxyurea

<b>HEMATOLOGICAL PARAMETERS</b>	<b>Baseline (N=45) % Mean (±SD) (Range)</b>	<b>After one year of therapy (N=45) % Mean (±SD) (Range)</b>	<b>p-value</b>
<b>Fetal Hemoglobin(%)</b>	15.52 (±9.14) 0.4-34.1	19.73 (±11.02) 0.7-44.6	<0.0001
<b>Hemoglobin(g/dl)</b>	8.58(±1.38) 6-12.2	10.30(±1.45) 7.3-15	<0.0001
<b>Mean Corpuscular Volume(fl)</b>	77.36 (±9.50) 60-96	90.45 (±7.67) 67.8-113	<0.0001
<b>Total Leukocyte Count(/µL)</b>	9795.55 (±4491.14) 4200-5000	6373.33 (±2498.67) 4000-18000	<0.001
<b>Platelet count (lac/µL)</b>	2.34 (±1.16) 1 - 5.16	2.21 (±0.96) 1 - 5	0.0609

**Table 3** Clinical response to hydroxyurea drug therapy in homozygous (SS) cases

<b>Clinical parameters</b>	<b>one year before starting hydroxyurea (N=36) Mean(±SD)</b>	<b>During one year of therapy (N=36) Mean(±SD)</b>	<b>Mean change [%mean change]</b>	<b>p-value</b>
frequency of vaso-occlusive crisis	11.02( ±6.76)	2.16(±3.36)	8.66 (±6.77) [78.58%]	0.0001
frequency of hospitalizations	2.11 (± 1.32)	0.44 (±0.73)	1.66 (± 1.35) [78.67%]	<0.0001
number of blood transfusions	0.33(± 0.79)	0.02 (± 0.16)	0.30 (±0.82) [90.90%]	0.0322
clinical score	11.86(± 1.77)	8.41 (±1.75)	3.44(±2.18) [29.00]	<0.0001

**Table 4** Hematological response to hydroxyurea drug therapy in homozygous (SS) cases

<b>Hematological parameters</b>	<b>Baseline (N=36) Mean ±SD</b>	<b>After one year of therapy (N=36) Mean ±SD</b>	<b>mean change [%mean change]</b>	<b>p-value</b>
fetal hemoglobin(%)	19.07 (±6.27)	24.25 (±6.83)	5.18 (±4.64) [27.16%]	<0.0001
Hemoglobin (gm/dL)	8.38 (±1.16)	10.21 (±1.53)	1.83 (±1.34) [21.83%]	<0.0001
Mean corpuscular volume(fl)	78.31 (±9.06)	90.56 (± 7.87)	12.259 (±9.94) [15.65%]	<0.001
Total leukocyte count(/µL)	10217.78 (± 4846.73)	6655.55 (±3433.43)	3562.22 (±3433.43) [34.86%]	<0.001
platelet count(lac/µL)	2.42 (±1.21)	2.26 (±1.03)	0.16 (±0.95) [6.61%]	0.3098 NS

**Table.5** Clinical response to hydroxyurea drug therapy in Sickle cell trait (AS) cases

<b>Clinical parameters</b>	<b>one year before starting hydroxyurea(N=9) mean(± SD)</b>	<b>During one year of therapy(N=9) mean(± SD)</b>	<b>mean change</b>	<b>p-value</b>
frequency of vaso-occlusive crisis	8.22(± 5.65)	1 (±1.22)	7.22 (± 5.86) [87.83%]	0.0061
frequency of hospitalizations	1.77(± 1.20)	0.24(± 0.72)	1.33 (± 0.72) [75.14%]	0.0114
number of blood transfusions	0.22(± 0.44)	0	0.22 (± 0.44) [100%]	0.1090
clinical score	11.33(± 1.41)	7.77(± 0.97)	3.55 (± 1.50) [31.33%]	<0.0001

**Table.6** Hematological response to hydroxyurea drug therapy in Sickle cell trait (AS) cases

Hematological parameters	Baseline (N=9) mean (±SD)	After one year of therapy (N=9) mean (±SD)	mean change	p-value
Fetal hemoglobin(%)	1.31 (± 1.77)	1.63 (± 1.89)	0.32 (±0.25) [24.42%]	0.0032
Hemoglobin (gm/dl)	9.35 (±1.92)	10.62 (± 1.13)	1.26 (±1.34) [13.47%]	0.0258
Mean corpuscular volume(fL)	73.55 (±10.82)	90 (±7.21)	16.44 (±5.46) [22.35%]	<0.001
total leukocyte count(/µL)	8106.66 (± 2038.11)	5244.44 (±1218.72)	2866.22(±1586.77) [35.35%]	0.0006
platelet count (lac/µL)	2.03 (±0.92)	2.0 (±0.60)	0.03(±0.40) [1.47%]	0.4096

**Table.7** Comparison of clinical and hematological response to one year of hydroxyurea therapy between SS and AS cases

variable	SS (n=36) Mean change (±SD)	AS (n=9) Mean change (±SD)	p-value
Frequency of VOC	8.66(±6.77)	7.22(±5.86)	0.6582
Hospitalizations	1.66(±1.35)	1.33(±0.72)	0.5293
Blood transfusions	0.30(±0.82)	0.22(±0.44)	0.5108
Clinical score	3.44(±2.18)	3.55(±1.50)	0.8864
Fetal hemoglobin (%)	5.18(±4.64)	0.32(±0.25)	0.0032
Hemoglobin (gm/dL)	1.83(±1.34)	1.26(±1.34)	0.0910
MCV (fL)	12.25(±9.94)	16.44(±5.46)	0.2332
TLC (/µL)	3562.22(±3433.43)	2866.22(1586.77)	0.7874

**Table.8** Co-relation of response of Clinical and hematological parameters with baseline HbF level

Sr. No.	Parameters	r-value	p-value
a.	Change in VOC*	0.0254	0.8687
b.	Change in Hospitalizations	-0.1094	0.4742
c.	Change in BT**	-0.0939	0.5394
d.	Change in Clinical score	-0.1575	0.3013
e.	Change in Hb <sup>Ⓢ</sup>	0.0392	0.7981
f.	Change in MCV <sup>Ⓜ</sup>	-0.3042	0.0422,S
g.	Change in HbF <sup>Ⓣ</sup>	0.1988	0.1905
h.	Change in Platelet count	-0.0427	0.7805
i.	Change in TLC <sup>ˆ</sup>	-0.1307	0.3921

\*VOC=vaso-occlusive crisis;\*\* BT= blood Transfusions; <sup>Ⓢ</sup>Hb=hemoglobin, <sup>Ⓜ</sup> MCV=mean corpuscular hemoglobin, <sup>Ⓣ</sup>HbF= fetal hemoglobin, <sup>ˆ</sup>TLC=total leukocyte count

**Table.9** Adverse drug reactions (all 54 patients were considered)

Sr. No.	System	Side effect	Cases (%) (N=54)
1	Hematology	Thrombocytopenia only	5 (9.25%)
		Leucopenia only	3 (5.55%)
		Thrombocytopenia+leucopenia	2 (3.7%)
		Pancytopenia	1 (1.8%)
2	Gastro-intestinal tract	Abdominal pain	2 (3.70%)
		Nausea	10 (18.51%)
3	Dermatology	Skin hyperpigmentation	5 (9.25%)
		Nail hyperpigmentation	6 (11.11%)
		Hair loss	1 (1.85%)
		Skin rash	1 (1.85%)
4.	Neurology	Vertigo	2 (3.7%)
5.	Others	Edema feet	1 (1.8%)
		Weight loss	1 (1.8%)

## Results

We recruited 54 cases; 2 cases developed severe adverse drug reactions and hence hydroxyurea was discontinued in them. 7 cases were not compliant with the drug. Remaining 45 cases were more than 90% compliant with the drug.

The study therefore comprised of 45 cases-36 cases of sickle cell disease and 9 cases of sickle cell trait. Mean age of cases was 22.97 years(range 13-42 years).16 males and 20 females were recruited in sickle cell disease(homozygous) cases while all 9 cases of sickle cell trait were females.

We observed that after starting hydroxyurea therapy, 23 out of 45 patients (51.11%) patients did not have further crisis. The mean frequency of vaso-occlusive crisis decreased by 81.54% during the one year of hydroxyurea therapy ( $p < 0.0001$ ). A total 38 out of 45 patients required hospitalization due to vaso-occlusive crisis before, but during one year of hydroxyurea therapy 15 out of 45 patients required hospitalizations. The mean frequency of hospitalizations due to vaso-occlusive crisis was decreased by 78.43%. The mean duration of hospital stay also decreased by 37.95% and it was statistically significant. Number of patients requiring blood transfusion decreased by 90% and mean frequency of blood transfusion decreased by 93.54%. the decrease in clinical score was 29.50% in sickle cell patients (both SS and AS pattern) which was statistically significant (table.1)

In the present study it was found that the baseline mean fetal hemoglobin level was 15.52 with the range 0.4-34.1. Fetal hemoglobin level after one year of hydroxyurea therapy was 19.73 with the range 0.7-44.6. The mean hemoglobin level increased significantly by 20.04% after hydroxyurea. The range of baseline hemoglobin in sickle cell patients (both SS and AS) was 6-12.2(gm/dl) and after one year of therapy was 7.3-15 (gm/dl). The MCV i.e. mean corpuscular volume of red cell increased by 16.92%. The total leukocyte count decreased significantly by

34.93% but the platelet count decreased by 5.55% and this was not significant.(table.2)

In homozygous sickle cell cases (SS), mean frequency of vaso-occlusive crisis, frequency of hospitalizations, blood transfusions and clinical score decreased significantly by 78.58%, 78.67%, 90.90% and 29.00% respectively with one year of hydroxyurea therapy. Similarly, mean fetal hemoglobin, hemoglobin, mean corpuscular volume significantly increased by 27.16%, 21.83% and 15.65% respectively with one year of hydroxyurea therapy. Total leukocyte count decreased significantly by 36.86%. The platelet count also decreased by 6.61% but it was not significant. (table.3 and 4)

In heterozygous sickle cell cases (AS), mean frequency of vaso-occlusive crisis, frequency of hospitalizations and clinical score significantly decreased by 87.83%, 86.44% and 31.42% respectively with one year of hydroxyurea therapy. But the decrease in the requirement of blood transfusions was not found to be statistically significant. Similarly, mean fetal hemoglobin, hemoglobin, and mean corpuscular volume significantly increased by 24.42%, 13.47% and 22.35% respectively with one year of hydroxyurea therapy. Total leukocyte count decreased significantly by 35.35%. The platelet count also decreased by 1.47% but it was not significant. (table.5 and 6)

When the clinical and hematological response to hydroxyurea therapy was compared between SS and AS cases, though there was decrease in frequency of vaso-occlusive crisis, frequency of hospitalizations, blood transfusions and clinical score in both, the difference between the two groups was not statistically significant. Fetal haemoglobin increased in both the groups and the mean change in HbF was significantly high in SS cases.(table.7)

Correlation of the change in clinical and hematological parameters after one year of hydroxyurea therapy with baseline fetal hemoglobin level demonstrated that change in

mean corpuscular volume had a negative correlation and it was statistically significant.

There was positive correlation of change in vaso-occlusive crisis, hemoglobin level and fetal hemoglobin with baseline fetal hemoglobin, but it was not statistically significant. There was negative correlation of change in hospitalizations, blood transfusion required, clinical score, platelet count and total leukocyte count with baseline fetal hemoglobin level, but this was also not statistically significant.(table.8)

In the present study, total 54 cases fulfilling eligibility criteria, were initially recruited in the study. 2 cases developed severe adverse drug reaction- One had severe bone marrow suppression and the other developed generalized vasculitic skin rash. 3 patients had nausea and skin pigmentation and they stopped hydroxyurea on their own.4 cases were noncompliant. When all 54 cases were considered, hematological adverse drug reaction was noted in 11 out of 54 i.e. 20.37%. These included thrombocytopenia, leucocytopenia, thrombocytopenia with leucocytopenia and pancytopenia. Following this was gastrointestinal side effects seen in 10 out of 54 cases (18.51%). These included abdominal pain and nausea in two cases and nausea in eight cases. Dermatological side effects were seen in 8 cases (14.81%). These included skin hyperpigmentation, nail pigmentation, hair loss and skin rash .Vertigo has been observed in 2 (3.7%), edema feet in 1 (1.8%) and weight loss in one case (1.8%). (table.9)

### Discussion

Sickle gene is an example of balanced polymorphism. It is nature's way of resisting malarial parasites. Mode of inheritance is autosomal recessive. Most of the patients with sickle cell disease suffer from intermittent episodes of vaso-occlusion due to sickled red blood cells in connective and musculoskeletal structures resulting in painful ischemia manifested as acute pain and tenderness, fever, tachycardia and anxiety. These recurrent episodes, called

painful/vaso-occlusive crises have also been reported in sickle cell trait patients.

Fetal Hemoglobin (HbF) level has been a useful criterion in predicting the clinical severity of sickle cell disease. Higher HbF levels are associated with lesser clinical severity in sickle cell anemia patients .<sup>10</sup>

Hydroxyurea has been used in the treatment of leukemia. It was observed that hydroxyurea stimulated HbF production and this led to clinical studies of hydroxyurea in sickle cell disease. Hydroxyurea has become the primary drug for reducing vaso-occlusive crises and improving the quality of life of sickle cell disease and is also used for increasing fetal hemoglobin in HbC/S patients. It is given in the dose of 10mg/kg per day and titrated upwards in sickle cell disease.<sup>4</sup>

Hydroxyurea has various effects-the most important is increase in HbF level. It also increases the total haemoglobin and hematocrit. It increases the mean corpuscular volume of red blood cells and improves their hydration resulting in better lifespan of the cell. The decrease in haemoglobin polymerisation improves red cell rheology.It is also reported that there is a reduction in expression of adhesion molecules on the surface of red blood cell. High neutrophil counts are associated with worse clinical prognosis and early death. Neutrophils adhere to vascular endothelium, impeding flow of the sickled red cell, increase blood viscosity and release inflammatory cytokines; activation and production of toxic oxygen radicals has also been reported. Hydroxyurea decreases the marrow production of neutrophils and exerts beneficial effect. It is also a nitric oxide (NO) donor. Nitric oxide maintains vascular tone and improves endothelial function.<sup>11,12,13</sup>

The present study of 45 cases (36 homozygous and 9 heterozygous) of sickle cell disease observed statistically significant improvement in clinical parameters namely, frequency of VOC's, frequency of hospitalization for VOC's, duration of hospital stay, requirement of blood transfusion and clinical score. Though published data on

vasoocclusive crisis in sickle cell trait is limited, 20% of our cases with painful crisis were HPLC proven sickle cell trait. 51.11% of our cases did not have further crisis. Mean frequency of VOC's decreased by 81.54% during one year of hydroxyurea therapy.

Studies by Italia. K., Singh. H, and Jain.D. have observed similar response.<sup>9,14,15,16,17</sup>

In accordance with the Arabian-Indian haplotype, the baseline fetal haemoglobin was 15.52±9.14. It increased significantly by 27.06% at the end of one year therapy. The total hemoglobin, mean corpuscular volume significantly increased in both homozygous (SS) and heterozygous (AS) cases and the total leukocyte count significantly decreased in both the groups. Thus statistically significant clinical and haematological response was obtained despite high level of Hb F. This highlights the pleiotropic and salutary effects of hydroxyurea.

Arabian study by Ali.Hal-Jama and Indian studies by Italia.K, Singh.H, and Jain.D. on homozygous cases have reported similar findings.<sup>7,9,14,15</sup>

Heterozygous sickle cell studies by Italia. K, Patel. S, Miller. M. Kand Yates .A.M have also reported clinical and haematological improvement similar to our observations.<sup>6,9,18,19</sup>

Hydroxyurea treatment was effective in homozygous as well as heterozygous sickle cell cases. Vaso-occlusive crisis has been consistently observed over many years in some cases of heterozygous sickle cell. No significant difference was observed in clinical and haematological response between the two groups except HbF response. HbF increased in both, but the rise in SS cases was significantly higher than AS cases. It may be inferred that the pleiotropic effects of hydroxyurea have contributed for improvement of VOC's in AS cases. Large sample size studies are required to evaluate the role of hydroxyurea in AS cases.

Clinical and haematological parameters were correlated with baseline HbF level. Only MCV negatively and statistically correlated with Baseline HbF level; a higher increase in MCV was

noted with lower baseline HbF level<sup>4</sup>. It may be inferred that clinical and haematological response to hydroxyurea therapy may not correlate with baseline HbF levels. Hydroxyurea therapy is therefore recommended in cases of sickle cell disease and trait.

Hydroxyurea was tolerated well in the present study; but regular monitoring is essential and drug may be discontinued if warranted.<sup>20</sup>

### Limitations

- 1) We could recruit only 9 sickle cell trait cases as against 36 of homozygous sickle cell cases.
- 2) The follow up duration of the study was one year. Longer duration of follow up is warranted in order to study long term effects of hydroxyurea in sickle cell cases.
- 3) Detailed structural studies of hemoglobin and genetic analysis is indicated in heterozygous cases (AS pattern) presenting with severe painful crisis.

### Conclusions

- 1) Hydroxyurea is effective in the management of homozygous sickle cell cases (SS pattern);. Hydroxyurea therapy results in statistically significant clinical and hematological response.
- 2) Hydroxyurea is effective in the management of heterozygous sickle cell cases; (AS pattern- sickle cell trait). Hydroxyurea therapy results in statistically significant clinical and hematological response Studies recruiting large number of heterozygous (AS pattern) cases are recommended.
- 3) Despite high levels of fetal hemoglobin, hydroxyurea exerts its benefits through hemorheological mechanisms.
- 4) Major adverse drug reactions were noted in 2 cases in the form of severe marrow suppression and generalized vasculitic rash. The drug was well tolerated otherwise. We emphasize that the treatment with hydroxyurea requires regular monitoring and follow up.



**Conflict of Interest:** The authors report no conflict of interest.

**Acknowledgement:** We sincerely acknowledge the guidance of Late. Dr. S.S. Agarwal (Assoc. Prof. of Medicine, IGGMC).

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