Original Article

Impact of hydroxyurea therapy on clinicohematological parameters in children with sickle cell anemia

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ABSTRACT

Background: Sickle cell anemia (SCA) is an autosomal recessive disorder associated with high morbidity and mortality in children. Hydroxyurea (HU) has shown to decrease the frequency of vaso-occlusive crisis, hospitalization, and blood transfusion in SCA patients. **Objective:** The objective of the study was to evaluate the efficacy of HU on clinical and hematological parameters in pediatric patients with SCA. **Materials and Methods:** A prospective analytic study was conducted among 49 children aged between 5 and 14 years, diagnosed with SCA visiting the outpatient department at a tertiary care center of Central India for over a period of 13 months. Children enrolled in the study were given HU and they were followed at every 2-month for 6 months. Clinical and laboratory parameters of the study population were recorded and analyzed. With nine children lost to follow up, the final analysis was carried in only 40 patients. **Results:** Most of the children (60%) belonged to the age group of 5–9 years and male predominance (70%) was observed in the study. Clinical parameters including number of hospitalization, vaso-occlusive crisis, and frequency of blood transfusion decreased significantly ($p<0.01$). After 6 months of HU therapy, there was increase in hemoglobin levels ($p=0.002$), decrease in total leukocyte count ($p=0.001$), and platelet count was observed ($p=0.283$). Improvement in the serum glutamic pyruvic transaminase and serum creatinine ($p<0.01$), serum bilirubin, blood urea, and serum glutamic-oxaloacetic transaminase ($p>0.05$) was observed. No adverse reactions were noticed during this study period. **Conclusion:** HU is an effective drug and can be safely used for the treatment in SCA.

Key words: Hemoglobin S, Hemoglobinopathy, Hydroxyurea, Sickle cell anemia, Vaso-occlusive crisis

Sickle cell anemia (SCA) is an autosomal recessive hemolytic anemia caused due to qualitative defect in the hemoglobin (Hb) B chain synthesis. A single-gene mutation causes the base pair change in B chain of Hb. In the presence of hypoxic condition, these changes result in red blood cell (RBC) breakdown. These sickle RBCs not only decrease RBC life span but also are responsible for numerous dreaded complications of sickle cell crisis [1]. Till date, no effective cure is available for this condition which indirectly affects the person's quality of life and life expectancy. Hydroxyurea (HU) mainly used as a chemotherapeutic agent has shown promising results in the treatment of SCA patients due to its disease-modifying effect [2-5]. It is now being recommended as an effective supportive therapy in SCA patients to decrease risk of life-threatening complications such as stroke [6]. HU is believed to increase HB F concentration in RBCs which has good oxygen carrying capacity. Increase in Hb F concentration decreases the proportion of Hb in blood, thereby reducing the chances of sickling and vaso-occlusive crisis [1].

Since HU is recommended in all patients with SCA, many studies have tested the efficacy of HU in SCA patients. Results from developed and developing countries reported that HU is a safe and very effective treatment to prevent complications in SCA and it can be given at low doses for a longer duration [2,3]. It is a well-tolerated medication with few side effects such as gastrointestinal discomfort, skin and nail hyperpigmentation, and transient and reversible myelosuppression. Limited studies are available in India evaluating the efficacy of HU in SCA [7,8]. The prevalence of SCA is significantly higher in Central India, with an increased incidence of hospitalizations secondary to various complications of SCA. Therefore, it is important to observe effect of HU therapy on person's well-being as well as the benefits and risks of prolong use. In view of this, the present study was conducted to evaluate the impact of HU therapy on clinical, hematological, and laboratory parameters in pediatric patients with SCA.

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MATERIALS AND METHODS

The present study was a prospective analytic study conducted among 49 patients diagnosed with SCA in a tertiary care center of Central India. Children between the age group of 5 and 14 years who visited to the outpatient department or hospitalized in study center with SCA from August 2014 to September 2015 were screened. Children with a history of ≥3 episodes of vaso-occlusive crisis in a year, ≥3 episodes of blood transfusions in a year or with complications such as acute chest syndrome, sequestration crisis, and stroke were recruited for the study. Patients with sickle cell trait or other hemoglobinopathies, those already on HU therapy and those with obvious contraindication (myelosuppression, other myelosuppressive therapy, or deranged serum creatinine), children with poor compliance, and not giving consent were excluded from the study.

After recording the baseline clinical and laboratory parameters, enrolled patients were started on fixed low dose of HU (15 mg/kg/day) as per recommendation and no dose escalation was done during the study period. They were followed up for next 6 months and monitored for laboratory parameters and clinical events. Patients were monitored at least every 2 months to assess symptoms, compliance, toxicity, clinical adverse events, growth parameters, and laboratory parameters – complete blood count and liver and renal function tests. Effect of HU therapy on clinical presentation such as episodes of vaso-occlusive crisis, number of blood transfusions, hospital admission requirement, and other complications (acute chest syndrome, stroke, dactilitis, and sequestration crisis) and laboratory parameters was recorded and compared with baseline values. A total of nine patients were lost to follow up and hence final analysis was done among 40 patients who completed follow-up till 6 months.

All collected data were recorded and analyzed with the help of SPSS 20.0. Quantitative and qualitative variables were analyzed by calculating the mean, ratio, and percentage. Paired t-test was used to compare changes in various clinical and laboratory parameters before and after starting therapy. p≤0.05 was considered statistically significant.

RESULTS

During the study period, a total 49 patients were enrolled; however, nine children were lost to follow up. Therefore, the final analysis was performed with data obtained from 40 children. Majority of the patients (60%) belonged to the age group of 5–9 years, while the remainder 40% of children were aged 10 years or above. Males (70%) preponderance was observed with a male:female ratio of 2.3:1. Distribution of patients based on age and sex is summarized in Table 1.

Significant changes were observed in the hematological parameters following 6 months of HU therapy (Table 2). Mean Hb level before starting HU therapy was 8.56±1.04 g/dl while after 6 months, it was increased to 8.97±1.29 g/dl (p=0.002). Mean total leukocyte count (TLC) was decreased from 8097±2230 cells/mm^3 at initiation of HU therapy to 6457±1255 cells/mm^3 after 6 months

Table 1: Age and distribution of the study population

Age group	Male, n (%)	Female, n (%)	Total, n (%)
5–9 years	20 (50)	4 (10)	24 (60)
10–14 years	8 (20)	8 (20)	16 (40)
Total	28 (70)	12 (30)	40 (100)

Table 2: Comparison of the effect of hydroxyurea therapy on hematological parameters

Hematological parameter	Baseline	After 6 months	t-test	p-value
	Mean±SD	Mean±SD		
Hb (g/dl)	8.56±1.04	8.97±1.29	3.26	0.002
TLC (cells/mm^3)	8097±2230	6457±1255	5.92	0.001
Platelet count (lakh/mm^3)	2.4±0.70	2.1±1.6	1.08	0.283

TLC: Total leukocyte count, Hb: Hemoglobin

(p=0.001). Platelet count was 2.4±0.70 lakh/mm^3 at baseline and decreased to 2.1±1.6 lakh/mm^3 after 6 months of therapy. There was a decreasing trend in TLC and platelet count but reduction was within normal limits and no adverse reaction was noted and no dose modification was required. HU therapy was not stopped in any patient due to leukopenia or thrombocytopenia.

Table 3 summarizes the comparison of HU effect on laboratory parameters measured at baseline and at 6 months. Compared to baseline (0.73±0.13 mg/dl), there was a significant increase in the serum creatinine level at 6 months after HU therapy to 0.80±0.16 mg/dl; p=0.02. However, serum creatinine level did not cross upper normal level; therefore, treatment was not withheld in any patient. Similarly, significant difference was observed in the serum glutamic pyruvic transaminase (SGPT) levels between two intervals (47.87±18.3 IU/dl vs. 40.23±5.65 IU/dl; p=0.003). S. bilirubin level decreased from 2.35±0.91 mg/dl to 2.19±0.60 mg/dl (p=0.128). Insignificant increase in mean blood urea level was observed at 6 months (25.26±3.97 mg/dl vs. 28.33 ±2.68 mg/dl; p=0.090), while serum glutamic-oxaloacetic transaminase (SGOT) levels decreased comparatively (33.35±30.5 IU/dl–26.35±4.90 IU/dl; p=0.160). Decrease in the serum bilirubin level and normal SGPT and SGOT values suggested the improvement in clinical condition.

Frequency of hospitalization was significantly decreased after 6 months of starting therapy (1±1.37 vs. 0.22±0.42; p=0.001). Similarly, frequency of vaso-occlusive episodes (4.3±1.22 vs. 1.3±0.75; p=0.001) and blood transfusions (0.82±1.39 vs. 0.22±0.42, p=0.001) also significantly reduced with HU treatment (Table 4). No significant adverse reaction due to HU therapy was noticed during the study period and there was no need to stop or modify drug dose in any patients due to any reason.

DISCUSSION

SCA is an autosomal recessive hemoglobinopathy, which in deoxygenated condition results in serious complications requiring frequent blood transfusions in affected patients [1]. This genetic

Table 3: Comparative analysis of laboratory parameters

Laboratory parameters	Before HU therapy (Mean±SD)	6 months after HU therapy (Mean±SD)	t-test	p-value
S. bilirubin (mg/dl)	2.35±0.91	2.19±0.60	1.55	0.128
S. SGOT (IU/dl)	33.35±30.5	26.35±4.9	1.41	0.160
S. SGPT (IU/dl)	47.87±18.3	40.23±5.65	3.11	0.003
B. urea (mg/dl)	25.26±3.97	28.33±2.68	1.70	0.090
S. creatinine (mg/dl)	0.73±0.13	0.80±0.16	2.28	0.020

HU: Hydroxyurea, SGPT: Serum glutamic pyruvic transaminase, SGOT: Serum glutamic-oxaloacetic transaminase

Table 4: Effect of HU therapy on clinical profile of patients

Clinical parameters	Baseline Mean±SD	After 6 months Mean±SD	t-test	p-value
Vaso-occlusive crisis episodes	4.3±1.22	1.3±0.75	18.73	0.001
Number of blood transfusion	0.82±1.39	0.22±0.42	3.43	0.001
Number of hospital admission	1±1.37	0.22±0.42	4.46	0.001

HU: Hydroxyurea

disorder is prevalent in Central India and is associated with frequent hospitalization due to various complications. Colah *et al*. [9] reported that in Central India, the most common complication in babies are early and severe anemia requiring blood transfusions and septicemia, while in tribal communities in South Gujarat, no severe complications were reported. In the present study, vaso-occlusive crisis was most common reason for hospitalization.

At present, HU is the only disease-modifying drug available for treatment in SCA which is found to be safe and effective in many studies [2-5]. In addition, it is proven effective in preventing painful episodes associated with SCA [1]. Improvement in the general well-being was due to increase in total Hb and HbF which is reported to have higher oxygen carrying capacity, thereby, decreasing the risk of sickling in RBCs and subsequent associated serious consequences [10]. The present study found that children with SCA showed significant improvement in clinical profile and laboratory parameters after initiating HU therapy. Similar improvement in conditions and decreased need for hospitalizations has been reported in the literature. Authors of the BABY HUG and HUSSOFT extended study conferred that HU is an effective drug which can be advocated for prolong periods in infants and children with SCA [2,3].

Kinney *et al*. [2] reported that hematological parameters (Hb, Hb F, mean corpuscular volume, and mean corpuscular Hb) improved significantly, while the laboratory toxicities were mild, transient, and reversible on temporarily discontinuation of drug. In Switch trial, authors compared the efficacy of HU with repeated blood transfusion in the management of stroke. Authors concluded that HU therapy was more effective in view of decreasing incidences of stroke and other acute complications such as pain, dactilitis, and acute chest syndrome.. In addition, HU therapy also decreased need of blood transfusion [6]. HUSOFT extension study documented sustained HbF levels, averaging 20% at 6 years after HU initiation [3]. Various other studies from all over world have also validated the aforementioned findings including the improvement in clinical condition, decreased need of blood transfusion, and hospitalization [7,11,12].

HU is very effective drug in decreasing chances of vaso-occlusive crisis as reported in literature [1]. Studies by Jain *et al*. [7], Patel *et al*. [8], and Sliva-Pinto *et al*. [12] reported a significant reduction in frequency of painful crisis with usage of HU. Results of our study are in accordance with these findings. Children and caregivers in our study reported that episodes of pain decreased and numbers of vaso-occlusive crisis decreased significantly after starting HU therapy. It is well known that HU increases HbF and total Hb level [1,10]. Similar to studies by Pondugala *et al*. [13] and Deshpande *et al*. [14], we observed a statistically significant increase in the total Hb level with HU therapy. Raised Hb level after starting HU therapy may be due to reduction in RBC destruction due to hemolysis.

HU when used in the management of leukemia's and other malignancies as a chemotherapeutic agent can significantly reduce platelet, RBC, and leukocytes levels but has no significant effect during the treatment of SCA [2-4]. Low-dose HU therapy in SCA was not associated with any significant changes in laboratory parameters in the present study, similar findings were reported in other studies by Jain *et al*. [7], Silva-Pinto [12], Deshpande *et al*. [14], and Keikhaei *et al*. [15]. Decreased level of leukocyte and platelet count noticed in the present study on follow-up as in other studies [16,17]. TLC was also decreased significantly but not as much to interrupt therapy [12,14]. Similarly, reduced platelet count following therapy observed in our study was not statistically significant.

In the present study, while significant increase in serum creatinine levels was observed, the rise in blood urea level was not statistically significant. Liver enzymes and bilirubin level decreased to normal levels. HUG KIDS trials [2] and another Indian study by Jain *et al*. [7] reported rise in blood urea level and change in liver functions. They also reported that transient and reversible changes including deranged liver functions (n-6), abnormal renal function test (n-4), thrombocytopenia (n-4), and immunodeficiency (n-1) were observed in 16 patients during the study period requiring cessation of therapy for a short period. On the contrary, no adverse reactions were reported during our study period and none of the patients required dose adjustment or stoppage of HU treatment. Small sample size and short duration of the study are a few of the limitations of the study which cannot be ignored. Long duration follow-up study should

be planned with larger sample size to verify findings of the current study.

CONCLUSION

With the results of the present study, it can be inferred that administration of HU in SCA patients improves clinical and laboratory profile, and decreases the risk of complications. Since the drug is well tolerated and effective in patients with SCA, HU can be safely implemented in the management strategy of SCA.

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