Original Article

Short-term safety and beneficial effects of hydroxyurea therapy in children with sickle cell disease

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ABSTRACT

Introduction: Worldwide, sickle cell disease (SCD) is the most common hemoglobinopathy among which SS pattern is more common. Although hydroxyurea (HU) is approved by the Food and Drug Administration for the treatment of recurrent moderate-to-severe painful crises in pediatric sickle cell anemia, there is a fear of toxicities. **Objectives:** The objectives of the study were to evaluate the short-term safety and beneficial effects of low-dose HU therapy in SCD (SS pattern) children. **Materials and Methods:** This prospective cohort study enrolled 40 cases of severe SCD and started HU in a fixed dose of 10 mg/kg/day. During follow-up, cases were evaluated for compliance of HU, its toxic effects and adverse events from their histories, clinical examinations, and laboratory parameters. Furthermore, beneficial effects of HU therapy were evaluated by assessing blood transfusion rate, frequency of painful events, strokes, acute chest syndrome, avascular necrosis of femur, and estimation of hemoglobin F (HbF) level after 2 years of therapy. HU was discontinued temporarily if any toxicity or minor adverse drug events occurred during therapy and was restarted at the same dose after normalization of deranged laboratory parameters. **Results:** The clinical adverse drug events seen were nausea (8.33%), diarrhea (2.78%), and hematuria (2.78%). The most common hematological toxicity was anemia and thrombocytopenia. Renal and hepatic toxicities were transient in nature. The mean acute painful events and blood transfusion rate reduced significantly on HU therapy. It increased Hb and HbF level significantly in SCD children. **Conclusion:** HU is a safe drug without significant toxicity or adverse events in a dose of 10 mg/kg/day for short duration and it is beneficial in SCD (SS pattern) children in reducing acute painful events and decrease blood transfusion rate.

Key words: *Beneficial effects, Safety of hydroxyurea, Sickle cell disease*

Worldwide, sickle cell disease (SCD) is the most common hemoglobinopathy among which SS pattern is more common [1]. Sickle cell anemia has the highest predicted frequencies of up to 10% spanned in Central India and India ranked the second-worst affected country in terms of predicted sickle cell anemia births [2]. In December 2017, the Food and Drug Administration approved hydroxyurea (HU) in pediatric sickle cell anemia from 2 years of age in recurrent moderate-to-severe painful crises [3].

Few observational studies in children suggested that HU was safe and beneficial [4-6]. Among the short-term side effects of HU, hematological toxicity was reported in a majority of studies, which include cytopenia and/or significant decrease in total white blood cell, platelet, and absolute reticulocyte counts (ARC) which are dose dependent, requiring dose reduction or temporary discontinuation of HU. Furthermore, a transient increase in transaminase activity, serum creatinine, skin rash, nausea, hair loss, diarrhea, idiopathic thrombocytopenic purpura, and renal failure in systemic lupus erythematous syndrome has been reported [7].

The present study evaluated the various toxicities/adverse drug events and beneficial effects by clinical, hematological, and biochemical parameters in children with SCD treated with HU therapy.

MATERIALS AND METHODS

This study was a prospective longitudinal follow-up study conducted over a period of 2 years. After obtaining clearance from the Institutional Ethical Committee and informed consent from parents or guardians, 40 children of severe SCD (SS pattern) of either sex between 5 and 15 years of age attending sickle cell clinic/pediatric outpatient department were enrolled. The indications to start HU therapy were two or more acute painful events per year requiring hospitalization, frequent blood transfusions (>3/year), one episode of previous acute chest syndrome, at least one episode of cerebrovascular event, and at least one episode of avascular necrosis of femur. The exclusion criteria were SCD children <5 years age, other systemic illness,

regularly on drugs such as theophylline, estrogen or calcium channel blockers, deranged hematological/renal/hepatic laboratory parameters, and parents not willing for participation.

Considering the expected toxicity thrombocytopenia which was 8.3% (Kinney *et al*. [4]) precision 10%, desired confidence level (1−α) 95%, minimum sample size required was 30 with 10% lost to follow up. Total sample size required was 33. However, 40 subjects were enrolled.

Required sample size (n): $n = \frac{(Z_{1-\alpha/2})^2 \times p \times (1-p)}{d^2}$

n=33, p=Expected toxicity, d=Absolute precision, α=Significance level=5%, $Z_{1-\alpha/2}$=1.96.

At enrollment, a detailed history of previous symptoms, hospitalizations, blood transfusion rate, frequency of vaso-occlusive crises, acute painful events, acute chest syndrome, avascular necrosis of femur, and stroke was elicited. The same was noted on follow-up visits. The laboratory parameters assessed at baseline and follow-up visits were hemoglobin (Hb), absolute neutrophil count (ANC), ARC, platelet count (Plt. C), hemoglobin F (HbF) level and serum glutamic-pyruvic transaminase (SGPT)/alanine aminotransferase (ALT), and serum creatinine level. Enrolled cases were treated with HU in a fixed dose of 10 mg/kg once daily. During the follow-up visits, cases were evaluated for compliance of HU, its toxic effects, adverse events from histories, and clinical examination. HbF levels were estimated after the completion of 2 years of HU therapy.

Hematological toxicity was defined as one or more of the following: (i) Hb – 20% decrease from entry/previous value or Hb <4.5 g/dl, (ii) ANC <2.0 × 10^3/mm^3, (iii) ARC <80 × 10^3/mm^3 unless Hb was 9.0 g/dl or higher, and (iv) Plt. C <80 × 10^3/mm^3. Biochemical toxicity was defined as Hepatic toxicity ALT/SGPT >twice the upper limit of baseline renal toxicity serum creatinine >1.0 mg/dl. Any toxicity or minor adverse drug events were managed as per the standard protocols [4]. HU when withheld for mean duration of 2 weeks period and restarted at the same dose after normalization of the deranged laboratory parameters. Statistical software STATA version 10.0 was used for statistical analysis.

RESULTS

In this study, most children belonged to 12–15 years (55%), 9–11 years (22.5%), and 5–8 years (22.5%) age groups. There were 22 (55%) males and 18 (45%) females belonging to Mahar, Teli, Kunbi, Muslim, and Gond community. Indications to start Hydroxyurea were the acute painful events ≥2/year requiring hospitalization (52.5%), frequent blood transfusions ≥3/year (27.55%), stroke (15%), acute chest syndrome (2.5%), and avascular necrosis of femur (2.5%). Out of 40 cases, 36 (90%) cases had completed regular monthly follow-up for 2 years while 4 (10%) cases were lost to follow up. Further, statistical analysis was performed on 36 cases only.

During hydroxyurea therapy, clinical events and toxicities were noted as shown in Table 1. The clinical adverse drug events observed in our study were nausea in 3 cases (8.33%), diarrhea in 1 (2.78%), and hematuria in 1 case (2.78%).

As shown in Table 2, the mean acute painful events and blood transfusions rates reduced significantly at the end of 2 years of HU therapy (p=0.001). No recurrence of acute chest syndrome or occurrence of stroke event was seen. The mean Hb and mean HbF level increased significantly after HU therapy. The reduction

Table 1: Clinical events and toxicities observed during hydroxyurea therapy

Clinical events and toxicities	Follow-up visits								Total events	Cases (%)
	1st	2nd	3rd	4th	5th	6th	7th	8th		
Acute painful events	11	13	0	10	0	5	1	3	43	30 (83.33)
Acute chest syndrome	0	0	0	0	0	0	0	0	0	0
Stroke	1	2	0	0	0	0	0	0	3	2 (5.56)
Avascular necrosis of femur	0	1	0	0	1	0	0	0	2	1 (2.78)
Splenic sequestration crises	3	2	1	2	0	4	2	0	14	6 (16.7)
Hemolytic crises	4	6	0	2	2	1	2	0	17	11 (30.6)
Aplastic crisis	0	0	1	0	0	0	0	0	1	1 (2.78)
Acute febrile illness	0	1	1	0	1	1	0	0	4	3 (8.33)
Pneumonia	0	0	0	1	0	0	0	0	1	1 (2.78)
Osteomyelitis	0	0	0	0	1	0	0	0	1	1 (2.78)
Cholelithiasis	0	0	0	0	1	1	0	0	2	2 (5.56)
Toxicities										
Anemia	1	1	1	2	0	1	1	0	7	5 (13.89)
Neutropenia	0	2	1	0	0	0	0	0	3	3 (8.33)
Reticulocytopenia	0	0	0	0	0	0	0	0	0	0 (0)
Thrombocytopenia	2	1	1	1	0	1	1	0	7	4 (11.11)
Renal toxicity	2	0	0	0	0	2	0	0	4	4 (11.11)
Hepatic toxicity	1	1	0	1	0	0	0	0	3	3 (8.33)

Table 2: Comparison of sickle cell disease-related clinical events and laboratory parameters before and after hydroxyurea therapy (n=36)

Clinical events and laboratory parameters	Before therapy		After 2 years		p value
	Mean	SD	Mean	SD	
Clinical events (per year per person)					
Acute painful events	2.11	0.94	0.25	0.5	0.001
Blood transfusion rate	1.88	1.36	0.30	0.57	0.001
Acute chest syndrome	0.027	0.16	0.027	0.16	1.00
Strokes	1.66	0.37	0	-	-
Avascular necrosis of femur	0.027	1.66	1.66	0.37	1.00
Laboratory parameters					
Hemoglobin (g/dl)	9.14	1.19	9.27	1.26	0.0012
Absolute neutrophil count ($\times 10^3/mm^3$)	4.22	1.56	4.05	1.60	0.5581
Absolute reticulocyte count ($\times 10^3/mm^3$)	163.52	78.48	144.42	64.02	0.2821
Platelet count ($\times 10^3/mm^3$)	258.80	81.39	262.21	94.76	0.8523
Serum glutamic-pyruvic transaminase/alanine aminotransferase (IU/L)	22.75	6.56	22.27	6.38	0.7353
Serum creatinine (mg/dl)	0.64	0.12	0.57	0.20	0.0728
Hemoglobin F (%)	17.80	5.73	18.13	5.79	0.001

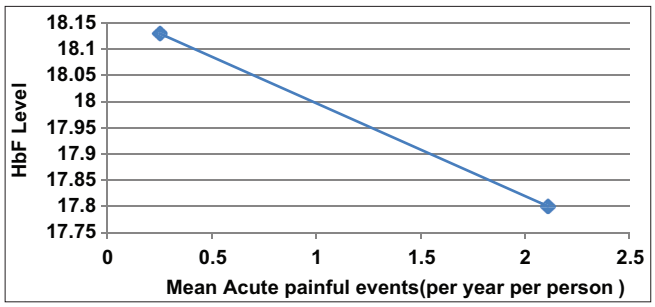

Figure 1: Correlation of acute painful events with hemoglobin F level on hydroxyurea therapy

in mean acute painful events statistically correlated with rising mean HbF level after HU therapy (correlation coefficient=0.3954, p=0.0170), as shown in Fig. 1.

DISCUSSION

Many studies demonstrated a beneficial effect of HU in SCD children [4-6]. Our study included 5–15-year-old SCD patients with severe painful crisis (>3 vaso-occlusive events/year) similar to the studies done by Kinney *et al*. [4], Scot *et al*. [6], and Ferster *et al*. [8]. In the present study, HU was given in a single fixed dose of 10 mg/kg/day orally without escalation due to fear of toxicity in pediatric age group. Similarly, Italia *et al*. [9] used HU 10 mg/kg/d and increased it up to 15 mg/kg/d. Lima *et al*. [10] used HU in an escalation dose of 10–20 mg/kg/d. Patel *et al*. [11]undertook study with minimal dose of HU (10 mg/kg/d) in pediatric and adult SCD patients.

Kinney *et al*. [4] in HUG-KIDS study used initial single oral dose of 15 mg/kg/d, which were increased by 5 mg/kg/d, if no toxicity was seen and the mean dose was 26.6±6.2 mg/kg/d. Tshilolo *et al*. [12] demonstrated safety and beneficial effects of HU in sickle cell anemia children in sub-Saharan Africa in a mean dose of 17±1.8 mg/kg/d. Opoka *et al*. compared HU (20±2.5 mg/kg/d) to placebo for 12 months and concluded that HU was safe for SCD children of sub-Saharan Africa, without increased severe malaria, infections, or adverse events [13].

In our study, transient clinical adverse drug events were nausea (8.33%), diarrhea (2.78%), and hematuria (2.78%). Kinney *et al*. [4] also observed similar adverse clinical events. Jayabose *et al*. [14] also reported nausea in their study of HU in sickle cell anemia. In the present study, anemia was the most common transient hematological toxicity followed by thrombocytopenia and neutropenia. However, reticulocytopenia was not observed. Hematological toxicity was common and transient in nature as reported in many previous studies [4-6,14-17]. Kinney *et al*. [4] reported various cytopenias, namely, anemia, reticulocytopenia, neutropenia, and thrombocytopenia from HU. Thrombocytopenia was reported in the studies by other authors also [8,16-18].

Renal toxicity occurred in four and hepatic toxicity in three cases in our study. All these toxicities were transient requiring temporary discontinuation of HU. Hepatotoxicity was also reported in studies done by Kinney *et al*. [4] and Wang *et al*. [18]. Renal toxicity was not reported in most of the studies. Odievre *et al*. [7] mentioned that a 13-year-old girl developed acute renal failure when systemic lupus erythematous syndrome occurred and required hemodialysis and definitive cessation of HU treatment. PED-HUG study by Kinney *et al*. [4] showed that the effects of HU on kidney and liver functions were negligible during the study. All our cases were alive and no case of malignancy/leukemia or sustained myelosuppression was observed.

In our study, we found a significant reduction in the number of acute painful events/year/person and mean blood transfusions rate after HU therapy and similar observations were made in the previous studies also [4,6,8-11,16,19,20]. We also found a significant increase in HbF at the end of 2 years of HU therapy and the rise significantly correlated with the reduction of the painful events. Ferster *et al*. [15] showed that mean HbF in SCD pediatric patients on HU therapy raised from 4.7% to 15%. Similar rise in HbF was observed by other authors also [4,9-11,21].

The study had few limitations. The study involved only 40 cases and it was of short duration. Further studies incorporating larger sample size and long-term duration are needed to assess sustained efficacy, safety, and toxicity of HU therapy in SCD children.

CONCLUSION

HU is safe and effective in treating the children with SCD on a short-term basis in a fixed low dose of 10 mg/kg/day.

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