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Original Research Article

Effectiveness of Hydroxyurea Therapy on Compound Heterozygous State of Sickle Cell Thalassemia: A Prospective Observational Study

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Abstract

Introduction: Sickle cell (SC) disease, encompassing variants like SC anemia and HbSβ-thalassemia, results from genetic mutations in the β-globin gene. This study aimed to explore the clinical and hematological profile of SCβ-thalassemia patients and assess the effectiveness of hydroxyurea (HU) treatment in Indian patients with SCβ-thalassemia.

Methods: This prospective, open-label, observational study was conducted at <details of the study site were removed for blinded peer review> between October 2013 and 2015. Patients diagnosed with SCβ-thalassemia were included in this study.

Results: A total of 56 SCβ -thalassemia patients (28 children, 28 adults) were included. The most common clinical feature for HU therapy was vaso-occlusive crisis (VOC), observed in 48.2% of patients. The mean VOC frequency before treatment significantly decreased from 6.6 to 1.0 after treatment, indicating an 85.5% reduction (P<0.0001), followed by the reductions in mean blood transfusion (83.9%) and hospitalization (90.8%). There was a significant improvement in Hb levels from baseline to 24 months (8.3 g/dL to 9.7 g/dL; P<0.001). Myelotoxicity was observed in seven patients. The mean serum creatinine, total bilirubin, indirect bilirubin, direct bilirubin, and lactate dehydrogenase were decreased by 16.2%, 32.0%, 32.5%, 33.7%, and 35.2%, respectively, after treatment with HU.

Conclusion: This comprehensive analysis reveals the positive impact of HU therapy on hematological and biochemical profiles in patients with SCβ-thalassemia. These findings underscore the potential of HU therapy as an effective and well-tolerated treatment option.

Keywords: SCβ-thalassemia, Hydroxyurea, β-globin gene.

Introduction

Sickle cell β-thalassemia occurs when both the sickle cell gene and a β-thalassemia gene are inherited together, leading to a diverse set of inherited Hb disorders [1]. Current treatment strategies for SCβ- thalassemia primarily focus on supportive measures, including hydroxyurea (HU) therapy, transfusion support, and symptomatic management of complications [2].

Hydroxyurea functions as a cytotoxic, anti-metabolic, and antineoplastic agent while also promoting the synthesis of fetal hemoglobin (HbF) through the stimulation of γ-globin production [3]. Hydroxyurea is the most commonly recommended pharmacological therapy for patients with sickle cell disease (SCD) in both the pediatric and adult population. Fetal hemoglobin strongly influences the clinical and hematologic features of sickle cell anemia. Higher levels of HbF are associated with a reduced rate of acute painful episodes, fewer leg ulcers, less osteonecrosis, less frequent acute chest syndromes, and reduced disease severity. The percentage of HbF influences both laboratory values and clinical features in children and adults with sickle cell anemia [4]. A multi-site observational study investigated the connections between baseline and HU-induced HbF levels in children with SCD [5].

Previous studies have shown that HU is safe and effective in patients with HbSβ-thalassemia. It has exhibited a substantial decrease in both painful crises and acute chest syndrome in individuals affected by sickle cell anemia, resulting in a notable

reduction in hospitalizations [6,7,8]. Moreover, some studies have focused on low dose of HU (10 mg/kg/day), which are effective and safe in reducing the frequency of vaso-occlusive crises (VOC) and the requirement of blood transfusion in patients with both homozygous sickle cell anemia [9,10,11]. The clinical efficacy of HU in the reduction of sickle cell crisis, stroke incidence, chronic organ damage, and overall mortality has been reported [7, 12, 13]. There is limited data on the use of HU in SCβ-thalassemia with the Indian haplotype in both children and adults. Therefore, there is a need to assess the effectiveness of HU in this specific population. The present study was conducted to evaluate the efficacy of HU in Indian patients with SCβ-thalassemia across both age groups.

Methods

Study design: This prospective, open-label, observational study was conducted at <details of the study site were removed for blinded peer review> from October 2013 to October 2015. The study was approved by the ethical committee of the institute, and written informed consent was obtained from the patients before conducting the study.

Inclusion criteria: Patients with confirmed diagnosis of SCβ-thalassemia, based on comprehensive criteria, including a thorough examination of their medical history, clinical features, family study, and Hb electrophoresis, were included. The study specifically focused on individuals diagnosed with SCβ-thalassemia who required HU therapy.

Exclusion criteria: Heterozygous forms, pregnant females with SCβ-thalassemia, individuals not requiring HU, those previously treated with HU or other ant-sickling agents, patients with hepatic or renal insufficiency, hypersensitivity to HU therapy, non-compliance to HU, and patients in a myelosuppressive state were excluded from the study.

Study procedure: The sickling test and hemoglobin electrophoresis were initially conducted. Cases with S-band on electrophoresis underwent high performance liquid chromatography (HPLC). Patients showing HbA2 levels > 4% proceeded to molecular diagnosis (ARMS-PCR) and parental studies for confirmation of sickle β-thalassemia. Confirmed cases of sickle cell β-thalassemia underwent detailed clinical examination. Patients with ≥ 3 VOC or ≥ 2 BT in the last 12 months were treated with HU. Hydroxyurea-treated cases were regularly followed up every 3 months, and patients were encouraged to visit the sickle cell clinic. During each visit, patients were assessed for HU toxicity using a complete blood count (CBC), neutrophil count, liver function test (LFT), renal function test (RFT), and other investigations as needed.

Data Collection: For each patient, age, sex, chief complaints, history of present illness, past history, family history, and previous treatment history were recorded. A detailed general and systemic examination was performed to evaluate overall health.

Investigations

- Automated full blood counters were used to check the differential count (DC), total leukocyte count (TLC), hemoglobin (Hb), red blood cell count (RBC), hematocrit (HHC), mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH), mean corpuscular hemoglobin concentration (MCHC), total platelet count (TPC), and absolute neutrophil count (ANC).
- Total and direct bilirubin levels were determined using a modified Jendrassik and Grof method.
- Serum lactate dehydrogenase and creatinine levels were measured.

Definitions

VOC: Acute painful event that required oral or injectable analgesics and lasted for at least 4 hours when, when no other cause could explain the symptom [14].

Statistical analysis: The data was analyzed using Statistical Package for The Social Sciences (SPSS) software, version 23.0. Descriptive statistics, including mean and standard deviation (SD) was used to summarize demographic characteristics of the patients, while frequency and percentages were used for categorical variables. Paired sample t-test was used to compare pre- and post-treatment HbA1c levels. A $p<0.05$ was considered statistically significant.

Result

A total of 56 patients (28 children and 28 adults) with HbSβ-thalassemia were included in this study, with the majority being male (65.5%). The most common clinical feature for HU therapy was VOC (48.2%), followed by splenomegaly (33.9%), fever (26.8%), and anemia (23.2%) (Table 1).

Table 1: Clinical feature of the patient

Options	Number of patients (N=56)
Clinical feature	
VOC	27 (48.2)
Slenomegaly	19 (33.9)
Fever	15 (26.8)
Anaemia	13 (23.2)
Hepatomegaly	6 (10.7)
AVN	4 (7.1)
Jaundice	2 (3.6)
Dactilitis	2 (3.6)
Osteomyelitis	1 (1.8)
Data presented as n (%). AVN, avascular necrosis; VOC, vasso- occlusive crisis.	

The mean frequency of VOC before treatment was 6.6, which significantly decreased to 1.0 after HU treatment, representing an 85.5% reduction (P<0.0001). Additionally, the mean frequency of blood transfusions decreased by 83.9%, and the frequency of hospitalizations decreased by 90.8%. (Table 2).

Table 2: Clinical response to HU therapy

Clinical event	Number of patients		% Decrease	P value
	Pre HU	Post HU		
VOC	6.6 (4.8)	1.0 (1.1)	85.5%	<0.0001
BT	2.5 (3.7)	0.4 (1.3)	83.9%	<0.0001
Hospitalization	3.3 (3.6)	0.3 (0.8)	90.8%	<0.0001
Data presented as mean (SD) unless otherwise specified. BT, blood transfusion; VOC, vasso occlusive crisis.				

There was no significant difference in mean levels of HbA (4.8 vs 4.1 %F cells; P>0.05) and HbA_2 (5.1 vs 5.5 %F cells) from baseline to 24 months. The mean HbF level was 15.7 %F cells at baseline which was significantly increased to 23.9 %F cells at 24 months (P<0.001). The mean HbS level was significantly decreased from baseline to 24 months of treatment (72.9 vs 59.4 %F cells).

There was a significant improvement in mean levels of Hb from baseline to 24 months (8.3 g/dL vs 9.7 g/dL; P<0.001) (Table 3).

Table 3: HPLC parameter change after HU therapy

Options	Pre HU	3 Month	6 Month	9 Month	12 Month	15 Month	18 Month	21 Month	24 Month
HbA (% F cells)	4.8 (2.1)*	4.3 (1.0)*	4.2 (1.0)*	4.2 (1.0)*	4.3 (1.0)*	4.2 (9.0)*	4.0 (94.0)*	4.1 (97.0)*	4.1 (9.0)*
HbA_2 (% F cells)	5.1 (7.0)	5.2 (9.0)	5.4 (9.0)	5.5 (1.1)	5.4 (1.1)*	5.5 (1.1)*	5.5 (1.1)*	5.5 (1.2)*	5.5 (1.2)*
HbF (% F cells)	15.7 (6.7)**	20.9 (6.5)**	22.0 (6.5)**	23.4 (7.0)**	22.5 (6.8)**	23.3 (6.4)**	23.2 (6.32)**	24.1 (5.9)**	23.9 (6.2)**
HbS (% F cells)	72.9 (6.8)**	66.2 (6.4)**	69.6 (6.7)**	63.0 (6.5)**	65.51(5.9)**	61.8 (6.6)**	61.6 (6.1)**	60.4 (5.8)**	59.4 (7.2)**
Hb (g/dL)	8.3 (1.9)	9.3 (1.6) <0.05	9.7 (1.4) <0.001	9.6 (1.6) <0.001	9.5 (1.4) <0.05	9.9 (1.8) <0.001	9.6 (1.6) <0.001	9.8 (1.9) <0.001	9.7 (1.8) <0.001
Data presented as mean (SD). *>0.05; **<0.001. HbA, Hemoglobin A; HbA2, hemoglobin A2; HbF, fetal hemoglobin; HbS, sickle hemoglobin.									

Moreover, WBC count was significantly decreased from baseline (11.3 x $10^3/\mu L$) to 24 months (8.2 x $10^3/\mu L$; P<0.05). Myelotoxicity from HU therapy was observed in seven patients, of whom six showed a decrease in ANC level (<2500/µL) and one showed a decrease in TPC count (<80000/µL).

The mean serum creatinine was decreased by 16.2% after treatment with HU.

Similarly, the mean serum total bilirubin, indirect bilirubin, direct bilirubin, and lactate dehydrogenase decreased by 32.0%, 32.5%, 33.7%, and 35.2%, respectively, after treatment with HU.

Discussion

Hydroxyurea, known for enhancing γ-chain synthesis and HbF production, has proven effective in treating sickle cell anemia. However, there is limited knowledge regarding the effectiveness of this drug in β-thalassemic patients, especially in the Indian population [3, 15, 16]. HbSβ-thalassemia is the second most common Hb variant at VIMSAR, Burla, representing 4.5% of SCD cases. In India, 3-4% of the population carries β-thalassemia. The co-inheritance of sickle cell trait with β-thalassemia is less frequent but complicates disease management [17].

The safety and efficacy of HU therapy are well documented in the literature for use in both children and adults. Many prospective studies have investigated the efficacy of HU in patients with SCβ- thalassemia, reporting a significant increase in HbF levels and a reduction in the frequency of painful crises, acute chest syndrome, and hospitalizations [8, 18]. The meta-analysis demonstrated that HU has good clinical efficacy in increasing Hb levels and decreasing transfusion requirements in individuals with transfusion-dependent β-thalassemia [19].

In the current study involving 56 patients, 65.5% were male and 34.6% were female. Among the clinical features, VOC was the most prevalent (48.2%), followed by splenomegaly (33.9%) and fever (26.8%). The study conducted by Charache S, et al. reported that HU demonstrated a significant reduction in painful crises and acute chest syndrome among individuals with sickle cell anemia, leading to decreased hospitalizations [7]. Although another study found that HU therapy was beneficial in reducing the VOC, blood transfusion needs, and hospitalization requirements, there remains a significant gap in the documentation of HU for SCD in Indian patients [9].

One recent study demonstrated that administration of HU significantly reduced VOCs by 80%. Significant improvement was observed in Hgb, which increased by 13; WBC count decreased by 28%; MCV improved by 10%; and HgbF improved by 28%; platelet count decreased by 3% [20]. However, in the present study, the HU led to a significant reduction in VOC by 85.5%, blood transfusion by 83.9%, and hospitalizations by 90.8%, indicating the effectiveness of HU treatment.

The hematological responses to HU therapy were assessed through various parameters. In the study by Castro Lobo et al., which involved a group of 1,760 children aged 3 to18 years, it was observed that Hgb, MCV, and HgbF increased, while WBC and platelet count decreased over a 12-month period in 267 patients treated with HU therapy [21].

In another study 44 patients with thalassemia intermedia were treated with HU at a dosage of 10 mg/kg/day for one year. The results indicated that HU significantly reduced the rate of transfusion, hospitalization, spleen size, and the number of visits to specialists. Moreover, it improved the levels of Hb, MCH, HbF, and MCV [22]. However, in this study, the HPLC analysis revealed significant changes in hemoglobin levels over the 24-month treatment period. There was a significant decrease in HbS levels and an increase in HbF levels. These results indicate the beneficial effects of HU therapy on overall hematological health.

In the current study, myelotoxicity is a concern with HU therapy, and its impact on TPC and ANC was assessed. The results indicate a low incidence of myelotoxicity, with only one patient experiencing a decrease in TPC and six experiencing a decrease in ANC. These findings suggest that HU therapy is generally well-tolerated in the studied population.

The biochemical effects of HU therapy were evaluated through the levels of serum creatinine, total bilirubin, indirect bilirubin, direct bilirubin, and lactate dehydrogenase. Significant changes were observed in all these markers after HU treatment, suggesting an overall improvement in renal and hepatic function.

Conclusion

This study highlights the effectiveness of HU therapy in managing sickle cell disease and SCβ-thalassemia, especially in the Indian population. The positive clinical, hematological, and biochemical responses, along with a low incidence of myelotoxicity, underscore the potential of HU as a valuable therapeutic option in the management of SCβ-thalassemia.

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