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Original Article

Role of Hydroxyurea in Patients of Beta Thalassemia Major

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ABSTRACT

Objective: To study the role of Hydroxyurea in patients suffering from β-thalassemia major.
Study Design: Prospective longitudinal study.
Place and Duration of Study: Department Paediatrics, Combined Military Hospital, Malir Cantt, Karachi Pakistan, from Nov 2019 to Oct 2020.
Methodology: Data from 73 beta-thalassemia major patients was collected using a structured questionnaire containing inquiries about basic socio-demographic details, disease history, laboratory reports and particulars of former treatment regimens. Hydroxyurea was administered, and its effects were noted among the subjects regarding the frequency of transfusion, haemoglobin levels and severity of clinical symptoms.
Results: The mean age of study subjects was 9.15±3.99 years, and most study subjects (56.14%) were boys. The pre-intervention (before administration of Hydroxyurea) levels of Hemoglobin (Hb), mean corpuscular volume (MCV), mean corpuscular haemoglobin concentration (MCHC), and serum ferritin levels were unremarkable when compared to post-intervention levels. However, a significant difference was observed in HbF levels. In addition, an encouraging decrease was reported in the self-rated severity (using VAS) of symptoms such as fatigue ($p<0.05$), weakness ($p>0.05$), and shortness of breath ($p>0.05$). In addition, the transfusion interval was significantly reduced ($p<0.05$).
Conclusion: After carefully considering the results, it can be concluded that Hydroxyurea plays a positive role and brings about significant improvement among patients suffering from β-thalassemia major.

Keywords: Fetal hemoglobin, Genetic disease, Hydroxyurea, Thalassemia major.

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INTRODUCTION

Beta (β) thalassemia is an inherited disorder of the blood, which manifests when an individual cannot maintain the required amounts of the oxygen-carrying /transporting element of blood (haemoglobin) due to an underlying genetic abnormality.[1] The highest disease prevalence is in the thalassemia belt, a group of countries in the Middle East, Central Asia and South-East Asia.[2,3] Nearly 3% of the population in the world and 5-7% of the Pakistani population have the beta thalassemia gene, so they have a carrier status. Approximately 5 to 9 thousand children with β-thalassemia are born yearly in Pakistan, with approximately 9.8 million carriers living among the population.[4,5]

An important variant of the condition, β-thalassemia major, is the severest form of the disease, meriting routine transfusions of blood and elaborate, continuous medical care because of two damaged genes and a resultant complete lack of beta protein. Patients suffering from it need red blood cell transfusions as frequently as once in 2 to 3 weeks, which amounts to fifty-two units of blood annually.[6] This continuous and long-term practice causes an overload of Iron, which is deleterious to the body. Some more prone organs are in general and to the liver, heart, endocrine glands and joints. The adverse effects of continued blood transfusion and constraints of ample blood supply have long merited research for a more feasible solution to the problem.[7]

Hydroxyurea is a drug which increases fetal haemoglobin concentration by promoting γ-globin production via an underlying mechanism that is yet to be unearthed. It has shown substantial benefits to patients with sickle cell anaemia. It can potentially produce promising results in patients with beta-thalassemia major by decreasing transfusion requirement.[8] Marked benefits are expected among patients, owing to hiked γ-globin chain production and resultant neutralization of the α-chains in excess and correcting, to a partial extent, the ineffective erythropoiesis. Anaemia is also resolved to a significant extent among patients.[9,10] Considering this fact, we studied the role of HydroxySurea in patients suffering from β-thalassemia major to decrease the transfusion rate and its related complication.

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METHODOLOGY

This prospective longitudinal study was carried out at the Paediatric and Medicine Outpatient Department, Combined Military Hospital (CMH), Malir Cantt, Karachi Pakistan from November 2019 to October 2020. The Ethical Review Committee granted permission (Certificate No. 15/2020/Trg/Adm). The sample size of 73 beta-thalassemia major patients was calculated via the Openepi Sample Size calculator.[11]

Inclusion Criteria: All the patients of beta thalassemia major, aged 2 to 24 years receiving Hydroxyurea, were included in the study.

Exclusion Criteria: All the patients lost to follow-up, patients with non-adherence to Hydroxyurea, those with active liver and renal disease, and those on other therapy were excluded from the study.

Written informed consent was taken from each patient or their parents. The diagnosis of Thalassemia major was based on clinical presentations and haemoglobin electrophoresis report. All the study subjects received oral HU of the same brand with a dose of 10±5mg/kg per day for 24 weeks, and its effects were noted among the subjects in terms of frequency of transfusion, Hb levels and severity of clinical symptoms while maintaining an HB level of 9-10g/dl. Before HU administration, all study subjects were made to undergo necessary laboratory investigations, including a complete blood count (CBC) with serum ferritin. In addition, patients were advised to take folate and calcium supplements before initiating HU and during therapy.

All the data was collected using a structured questionnaire containing inquiries about basic sociodemographic details, laboratory reports and particulars of former treatment regimens. Statistical Package for Social Sciences (SPSS) version 20.0 was used for the data analysis. Quantitative variables were summarized as Mean±SD and qualitative variables were summarized as frequency and percentages. The Chi-square test was applied, and the *p*-value of <0.05 was considered significant.

RESULTS

The mean age of the study participants was 9.15±3.99 years, and most of the subjects (56.14%) were boys. Family history of the disease was common, with 23.29% of the subjects having siblings with beta-thalassemia major and 28.77% of the subjects with siblings suffering thalassemia minor. Average haemoglobin level, HbF and serum ferritin level were significantly raised after the intervention of Hydroxyurea (p<0.05). In contrast, average values of MCV, MCH and MCHS were statistically insignificant according to pre and post-intervention (p>0.05), as shown in Table-I.

Table-I Descriptive Statistics of Hematological Parameters and Ferritin Before and After Intervention (n=73)

Parameter	Pre-Intervention	Post-Intervention	*p*-value
Hemoglobin(g/dl)	7.9±0.69	9.10±1.4	0.001
Mean corpuscular volume (fl)	84.9±22.1	88.3±21.4	0.125
Mean corpuscular hemoglobin (pg)	27.8±5.1	27.9±6.9	0.860
Mean corpuscular hemoglobin concentration (g/dl)	33.2±8.1	32.8±7.8	0.582
Hemoglobin F (g/dl)	1.1±0.3	5±1.1	0.001
Serum ferritin (ng/ml)	5893±2103	4127±1913	0.001

Symptoms such as fatigability, weakness and breathlessness were significantly decreased after 24 days of administration of HU (p-0.001). In addition, post-Intervention, the need for blood transfusion decreased dramatically from 14 to 28 days (p-0.001), as shown in Table-II.

Table-II Comparison of symptoms and transfusion interval before and after Hydroxyurea administration (n=73)

Variables	Pre-Intervention	Post Intervention	*p*-value
Fatigue	7.5±1.3	4.1±2.1	0.001
Weakness	8.1±1.2	7.4±1.8	0.001
Shortness of breath	6.9±2.4	5.4±1.1	0.001
Transfusion interval	14±3	28±7	0.001

DISCUSSION

The backbone of the entire treatment of patients suffering from β-thalassemia major is routine blood transfusions and Iron chelator use. Reactivation of γ-globin genes pharmacologically holds great potential as a viable treatment alternative for thalassemia syndromes and other conditions such as sickle cell anaemia.[11] Studies by the Chatterjee *et al.* (2012) and Aleluia *et al.* (2017) showed that HU could provably up-regulate γ-chain synthesis and production of HbF.[12,13] HU has yielded positive outcomes when tested as a treatment for sickle cell disease by bringing about an increase in the levels of HbF,[14] and lessening the eventual adverse events of the disease and conventional treatment protocols.[15] However, experience with

this pharmacological alternative administration to β-thalassemia major patients is scarce. This research studied the role of Hydroxyurea administration in β-thalassemia major patients dependent on blood transfusion and noted that HbF alleviated symptoms of β-thalassemia. Furthermore, a marked increase in the HbF level was linked to a consequent decrease in the severity of negative symptoms of the disease regardless of gender.

Angelucci *et al.* (2016) suggested that a fall in serum ferritin levels among the subjects is also clinically very important, as iron overload significantly increases disease-related mortality and morbidity.[16] The decrement in serum ferritin burden is possible because of increased iron consumption for Hb synthesis as HU increases erythropoiesis overall, as is evident from the work of Italia *et al.* (2016) and Ghosh *et al.* (2018).[17,18] RBCs thus formed have improved survival as compared to those having alpha chain precipitates thus improving the effectiveness of erythropoiesis. HU was tolerated well by the study subjects, and no hematologic toxicity was observed in the short months of usage. However, long-term follow-up in extended usage is important. Our research, too, showcased that HU yields good results among patients of β-thalassemia major.

A similar study by Zamani *et al.* (2009) on HU therapy in patients with β-Thalassemia major also noted decreased serum ferritin as well as transfusion requirement over one year of treatment.[19] However, in contradiction, conclusive evidence was not found to support the use of HU in patients of β-Thalassemia major in some randomized controlled trials performed by Ansari *et al.* (2019), and Fong *et al.* (2016) did not find.[20,21]

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CONCLUSION

After carefully considering the results, it can be concluded that Hydroxyurea plays a positive role and brings about significant improvement among patients suffering from β-thalassemia major.

Conflict of Interest: None.

Author's Contribution

Following authors have made substantial contributions to the manuscript as under:

BF & STHZ: Study design, drafting the manuscript, data interpretation, critical review, approval of the final version to be published.

AS & MS: Data acquisition, data analysis, critical review, approval of the final version to be published.

MTN & WS: Conception, critical review, drafting the manuscript, approval of the final version to be published.

Authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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