IMPACT OF HYDROXYUREA ON BLOOD TRANSFUSION RATE IN PATIENTS OF BETA THALASSEMIA MAJOR

ABSTRACT

Objective: To determine the effectiveness of Hydroxyurea on blood transfusion rate in patients of Beta thalassemia major.

Material and methods: This cross-sectional study was held in the department of Genetics and Molecular **B**iology/Pathology department at LUMHS Jamshoro, and Diagnostic and Research Laboratory, Hyderabad, Sindh from February 2015 to August 2015. All Patients of Beta thalassemia major diagnosed on the basis of clinical history Hb Electrophoresis, and their parents Hb Electrophoresis. All the patients with other Haemoglobinopathies, and other genetic diseases.

Results: Mean age of the patients was 11.02+3.93 years and males were in majority 68.0%. Positive family history was in 56.2% cases. Mean serum Ferritin level was 12824.39±300.60ng/ml and mean hemoglobin level was 7.52±1.67 gm/dl. Few patients did not report follow up, because some families had migrated to others areas of Sindh, and some cases went to other welfare hospitals/ centers, for treatment, therefore, out of 40 patients, 30 were observed hydroxyurea and overall, this treatment showed a significant decrease in blood transfusion requirements (P-0.01).

Conclusion: As per study conclusion the hydroxyurea was observed to be the effective treatment to decrease the blood transfusion rate but patients should be treated under responsible and proper observation.

Key words: β Thalassemia, Hydroxyurea, transfusions

INTRODUCTION

β--Thalassemia, the most common genetic blood disorder, is caused by a deficiency in the formation of -globin chain, that resulting in inadequate erythropoiesis caused by an imbalance in the creation of alpha and non-alpha globin chains.[1] Though -thalassemia is frequent amongst people from the Mediterranean, central Asia, southern China, Middle East and India, it is no longer exclusive to these regions due to migration to other parts of the globe.[2,3] In general, around 5% of the worldwide population suffers from hemoglobin-related disorders, with thalassemia carriers accounting for around 1.7%.[4] Thalassemia affects about 5-8 percent of the Pakistani population, and approximately 5000 thalassemia major infants are born in Pakistan every year.[5] Regular blood blood transfusions are the standard treatment for B-TM, but in addition to the risk of transmitting blood-borne illnesses, blood transfusions gradually create iron overload in key organs like heart and liver, which could also lead to early mortality.[4,6] A hallmark of -thalassemia is an imbalance in the α/β-chain ratio, which can be lowered by trying to compensate for defaulted chain of β-globin molecule with improved productivity of the -globin, which eventually forms HbF, and this HbF initiation limits necessity for blood transfusions, as well as iron chelation, to avoid complications linked to overload of iron through transfusion therapy.[7,8] As a result, various medications have

been studied in try to lessen the need for transfusions. Hydroxyurea (HU), a foetal Hb inducer that reduces /-globin chain imbalance and is expected to treat chronic anaemia and reduce the requirement for blood transfusions, has shown effective.[2,9] Hydroxyurea, which seems to be a ribonucleotide reductase inhibitor, can improve hemolytic symptoms by increasing HbF synthesis and partially rectifying the imbalance between globin chains and non-globin chains.[1] However, because therapy response differs from patient to patient, it is recommended that numerous factors that influence treatment response be identified.[5] On the other hand, various factors, including genetic alterations, globin chain formation, XmnI polymorphism, and other biochemical parameters, are thought to have a role in the therapeutic response to HU.[1] This study has been conducted to determine the effectiveness of Hydroxyurea on blood transfusion rate in patients of Beta thalassemia major.

MATERIAL AND METHODS

This cross-sectional study was carried out in the department of Pathology/Molecular biology and Genetics department at LUMHS Jamshoro, and Diagnostic and Research Laboratory, Hyderabad, Sindh. Study duration was six months from February 2015 to August 2015. All the patient of Beta Thalassemia Major diagnosed on the Hb Electrophoresis, having Hb less than 7 g/dL and were on regular transfusion every 2-4 weeks were included. All the patients had other Hemoglobinopathies and other Genetic diseases were excluded. Patients were divided in two groups in equal numbers. Half of the patients underwent blood transfusion with treatment of hydroxyurea and half without hydroxyurea. After taking informed consent Hydroxyurea was started as range 8-14 mg/kg/day. A fixed attending hematologist visited the participants every two weeks to assess their clinical and analytical responses. They were clinically evaluated for any signs of new onset extramedullary hematopoiesis, such as hepatosplenomegaly or abnormalities in the facial bones. Complete blood count (CBC) was analyzed for basic hematological parameters by using automated cell analyzer (Sysmex XN 1000i Tokyo, Japan). The medicine was stopped if patients developed intolerance or if their laboratory tests revealed leucopenia, a low platelet count, or abnormal RFTs or LFTs. The LFT, CBC, RFT, and ferritin levels were evaluated on monthly during this time, as well as their height, weight, hepatic and spleen sizes. Patients' treatment responses and HU side effects were also tracked. In comparison to those who did not receive hydroxyurea treatment, treatment response was defined as the capacity to maintain hemoglobin above 9g/dl or a reduction of at least 50% of baseline transfusion requirements. All the data was collected via study proforma. Data was analyzed on (SPSS) version 26.

RESULTS

Mean age of the patients was found 11.02+3.93 years, ranging from a minimum of 8 years to maximum 20 years. males were higher than females, 68.0% compared to 32.0%. Positive family history was found in 56.2% of the cases, but 43.8% patients had no family history of thalassemia being present. This is unusually higher negative history of patients under study. The possible explanation can be the fact that many

patients were not aware of such cases in their families. Mean serum Ferritin level was 12824.39±300.60ng/ml. Mean hemoglobin level was 7.52±1.67 gm/dl. Table.1

In this study 10 patients did not report follow up, because some families had migrated to others areas of Sindh, and some cases went to other welfare hospitals/ centers, for treatment. Therefore, out of 70 patients, 30 were on treatment with hydroxyurea. Overall, this treatment has caused a significant decrease in blood transfusion requirements(P-0.01). Table.2

(G-C) mutated patients had particularly shown good response with use of hydroxyurea as seen by significantly reduced blood transfusion rate with significant difference (p-0.001). Table.3

Table.1 Descriptive statists of the demographic characteristics n=80

Variables		**Statistics**
Age (years)		11.02+3.93 years
Gender	**Males**	68.0%
	Females	32.0%.
Family history	**Positive**	45/56.2%
	Negative	35/43.8%
Serum Ferritin level		2824.39±300.60 ng/ml
Haemoglobin level		7.52±1.67 gm/dl

Table. 2 Average blood transfusion with and without hydroxyurea n= 70

Variable	Without hydroxyurea n= 40	With hydroxyurea n= 30	P- value
Blood transfusions (average)	2.2±2.3	1.1±1.4	0.01

TABLE: 3. Blood transfusion rate according to gene mutation with hydroxyurea n= 30

Genes	Decrease transfusion rate	No change Transfusion rate	P- value
IVS 1 - 5 (G-C)	14	03	
IVS 1 - 1 (G-T)	04	01	
Fr 8 - 9	01	00	
CD 30 (G-A)	01	01	0.001
Fr - 16 (-C)	01	01	
Fr 41 - 42	01	00	

Del 619	00	01
CD 5 (-CT)	01	00

DISCUSSION

In contrast to individuals who do not get hydroxyurea treatment, those with overt clinical manifestations of the disease may be BetaThalassemia homozygotes (Thalassemia major), presenting with severe transfusion-dependent anaemia from around 6 months of life.[5] In our study mean age of the patients was 11.02+3.93 years and males outnumbered females (68.0% compared to 32.0%). Consistently Asif N et al[5] reported that the out of all males were 56 and females were 44 of 1-16 years and the overall average age was 7.34±3.58 years. On other hand Kosaryan M et al[10] also found males in majority as 52%. Raza Set al[11] in their study noted 56.95% males and 43.05%. females. This gender-ratio difference in thalassemia patients is significant and justifies further analysis in view of thalassemia as the single-gene disorder transmitted through the recessive mode of inheritance.

In our study mean serum Ferritin level was found to be 2824.39±300.60 ng/ml. Azhar U et al[12] reported levels of Ferritin 4236.5 ng/ml, which is significantly higher than normally accepted levels. Ferritin is the body's principal iron-storage protein. the synthesis of it is regulated via iron levels via interactions between cytoplasmic proteins attached to messenger ribonucleic acid (mRNA), now known as iron regulatory proteins, and certain mRNA structures, known as iron-responsive elements.[13] Because it binds to and sequesters intracellular iron, it plays a crucial function in iron homeostasis. Serum ferritin testing is becoming a frequent clinical finding, with elevated concentrations being a common finding. Increased serum ferritin levels are related with or without iron overload in a wide range of genetic and acquired disorders. In beta-thalassemia trait comparative investigations, high concentrations of serum ferritin were found, and even individuals who've never been transfused had clinical and biochemical symptoms of hemochromatosis.[14-16]

In this series the best efficacy of Hydroxyurea (HU) treatment in patients with thalassemia, was evidenced in terms of significant transfusion reduction rate (p-0.001). Consistently Kosaryan M et al[17] found an excellent response in 44.7% of thalassemia major patients with the mean Hb of 10g/dl. The remaining patients needed transfusions less frequently after treatment with HU. The changes in Hb and HCT before and after HU were also statistically significant in their study (p <.0001). Another study conducted by Bradai M et al[18] noted that good improvement in hematology with HU and regression of extramedullary hematopoietic masses in β Thalassaemic cases. They also reported that a reduction in extramedullary haematopoiesis has resulted in decrease in size of spleen and decreased number of circulating erythroblasts. It has also been reported in some studies that the higher age at first transfusion and higher baseline Hb correlated with a better response.[19] In our study, the thalassaemic patients showed better response to HU as compared to the late first transfusion starters which is comparable with the findings of Ansari et al.[20] Furthermore, we identified IVS 1 - 5 (G-C) mutant individuals that responded well to Hydroxyurea treatment in terms of

decreases in the blood transfusion (p-0.001), while IVS 1-1, on the other hand, had an equally positive response (G-T). However, a limited sample size does not allow for firm conclusions to be formed.

CONCLUSION

As per study conclusion the hydroxyurea was observed to be the effective treatment to decrease the blood transfusion rate but patients should be treated under responsible and proper observation. This was a small sample size and single center study; hence further large-scale studies are recommended to assess the role of Hydroxyurea in reducing the frequency of transfusion among patients of β -thalassemia.

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