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 with 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, in Hyderabad, Sindh from February 2015 to August 2015. All Patients with Beta-thalassemia major were diagnosed on the basis of a clinical history of Hb Electrophoresis, and their parent's Hb Electrophoresis. All the patients with other Haemoglobinopathies, and other genetic disorders.

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% of cases. The mean serum Ferritin level was 12824.39±300.60ng/ml and the mean hemoglobin level was 7.52±1.67 gm/dl. Few patients did not report follow-up, because some families had migrated to other areas of Sindh, and some cases went to other welfare hospitals/ centers, for treatment, therefore, out of 40 patients, 30 were observed with hydroxyurea and overall, this treatment showed a significant decrease in blood transfusion requirements (P-0.01).

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

Keywords: β Thalassemia, Hydroxyurea, transfusions

INTRODUCTION

β--Thalassemia, the most common genetic blood disorder, is caused by a deficiency in the formation of -globin chain, which results 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 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 the defaulted chain of the 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 to try to lessen the need for transfusions. Hydroxyurea (HU), a fetal Hb inducer that reduces /-globin chain imbalance and is expected to treat chronic anemia 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 to 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 with 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. The study duration was six months from February 2015 to August 2015. All the patients with Beta-Thalassemia Major diagnosed with Hb Electrophoresis, having Hb less than 7 g/dL, and were on regular transfusion every 2-4 weeks were included. All the patients who had other Hemoglobinopathies and other Genetic diseases were excluded. Patients were divided into two groups in equal numbers. Half of the patients underwent blood transfusion with the treatment of hydroxyurea and half without hydroxyurea. After taking informed consent Hydroxyurea was started in the range of 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 an automated cell analyzer (Sysmex XN 1000i Tokyo, Japan). The medicine was stopped if patients developed an 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 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

The mean age of the patients was found 11.02+3.93 years, ranging from a minimum of 8 years to a maximum of 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% of patients had no family history of thalassemia being present. This is an 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. The mean serum Ferritin level was 12824.39±300.60ng/ml. The 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 other 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 the 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 anemia 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 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 the other hand, Kosaryan et al[10] also found males in the majority at 52%. Raza et 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 a 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 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. Its 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 a significant transfusion reduction rate (p-0.001). Consistently Kosaryan et al[17] found an excellent response in 44.7% of thalassemia major patients with a 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 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 hematopoiesis has resulted in a decrease in the size of the spleen and decreased the 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 a 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, limited sample size does not allow for firm conclusions to be formed.

CONCLUSION

As per the study's conclusion 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.

Ethical Approval:

As per international standard or university standard written ethical approval has been collected and preserved by the author(s).

Consent

As per international standard or university standard, patients' written consent has been collected and preserved by the author(s).

REFERENCES

1. Bordbar MR, Silavizadeh S, Haghpanah S, Kamfiroozi R, Bardestani M, Karimi M. Hydroxyurea treatment in transfusion-dependent β-thalassemia patients. Iranian Red Crescent Medical Journal. 2014 Jun;16(6).

2. Algiraigri AH, Wright NA, Paolucci EO, Kassam A. Hydroxyurea for nontransfusion-dependent β-thalassemia: a systematic review and meta-analysis. Hematology/oncology and stem cell therapy. 2017 Sep 1;10(3):116-25.

3. E.P. Vichinsky, Changing patterns of thalassemia worldwide. Ann N Y Acad Sci, 1054 (2005), pp. 18-24

4. Ravangard R, Mirzaei Z, Keshavarz K, Haghpanah S, Karimi M. Blood transfusion versus hydroxyurea in beta-thalassemia in Iran: a cost-effectiveness study. Hematology. 2018 Aug 9;23(7):417-22.

5. Asif N, Anwar T, Chaudary H, Mehmood K, Yaqoob N, Tahir M, Hassan K. Treatment response to hydroxyurea in beta thalassemia. JIMDC. 2014;392:48-52.

6. Choobineh H, Dehghani S, Alizadeh S., et al. Evaluation of leptin levels in major beta-thalassemic patients. Int J Hematol Oncol Stem Cell Res. 2009;3(4):1–4

7. Iqbal A, Ansari SH, Parveen S, Khan IA, Siddiqui AJ, Musharraf SG. Hydroxyurea treated β-thalassemia children demonstrate a shift in metabolism towards healthy pattern. Scientific reports. 2018 Oct 11;8(1):1-9.

8. Ansari SH, Shamsi TS, Ashraf M, Perveen K, Farzana T, Bohray M, Erum S, Mehboob T. Efficacy of hydroxyurea in providing transfusion independence in β-thalassemia. Journal of pediatric hematology/oncology. 2011 Jul 1;33(5):339-43.

9. Musallam KM, Taher AT, Cappellini MD, Sankaran VG. Clinical experience with fetal hemoglobin induction therapy in patients with β-thalassemia. Blood, The Journal of the American Society of Hematology. 2013 Mar 21;121(12):2199-212.
10. Kosaryan M, Vahidshahi K, Karami H, Ehteshami S. Effect of Hydroxyurea on Thalassemia Major and Thalassemia Intermedia in Iranian Patients. Pak J Med Sci 2009;25(1):74-78.
11. Raza S, Farooqi S, Mubeen H, Shoaib MW, Jabeen S. Beta thalassemia: prevalence, risk and challenges. International Journal of Medicine and Health Research. 2016;2(1):5-7.
12. Azhar U. Audit Of Beta-Thalassemia Cases At Sheikh Zayed Medical College/Hospital, Rahim Yar Khan. JSZMC 2015;6(2):811-815
13. Kannengiesser C, Jouanolle AM, Hetet G, Mosser A. A new missense mutation in the L ferritin coding sequence associated with elevated levels of glycosylated ferritin in serum and absence of iron overload. Haematologica 2009;94: 335-339
14.Fargion S, Taddei MT, Cappellini MD, Piperno A. The iron status of Italian subjects with beta-thalassemia trait. Acta Haematol.982; 68: 109-114.
15. Fargion S, Piperno A, Panaiotopoulos N, Taddei MT. Iron overload in subjects with beta-thalassaemia trait: role of idiopathic haemochromatosis gene. Br. J. Haematol.1985; 61: 487-490.
16. Piperno A, Mariani R, Arosio C, Vergani A. Haemochromatosis in patients with beta-thalassaemia trait. Br. J. Haematol. 2000;111: 908-914
17. Kosaryan M, Vahidshahi K, Karami H, Ehteshami S. Effect of Hydroxyurea on Thalassemia Major and Thalassemia Intermedia in Iranian Patients. Pak J Med Sci 2009;25(1):74-78.
18. Bradai M, Abad MT, Pissard S, Lamraoui F, Skopinski L, de Montalembert M, et al. Hydroxyurea can eliminate transfusion requirements in children with severe β thalassemia. Blood. 2003;102(4):1529– 30
19 Bradai M, Pissard S, Abad MT, Dechartres A, Ribeil JA, Landais P, et al. Decreased transfusion needs associated with hydroxyurea therapy in Algerian patients with thalassemia major or intermedia. Transfusion 2007; 47(10):1830–6.
20. Ansari S, Shamsi T, Siddiqui F, Irfan M, Perveen K, Farzana T, et al. Efficacy of hydroxyurea in reduction of pack red cell transfusion requirement among children having beta-thalassemia major. J Pediatr Hematol Oncol, 2007; 29: 743-46