



## **Impact of Hydroxyurea on Blood Transfusion Rate in Patients of Beta-Thalassemia Major**

**Sumair Memon<sup>a\*\*</sup>, Ikram Din Ujjan<sup>b#</sup>, Humaira Ashraf<sup>c\*</sup>, Tasneem Memon<sup>d\*</sup>,  
Faria Sana<sup>b†</sup> and Shujaullah Talib<sup>e\*</sup>**

<sup>a</sup> Department of Pathology, MMC, Mirpur Khas, Pakistan.

<sup>b</sup> Department of Pathology, Liaquat University of Medical & Health Sciences (LUMHS),  
Jamshoro, Pakistan.

<sup>c</sup> Department of Pathology, NICVD, Karachi, Pakistan.

<sup>d</sup> Department of Paediatric, Roshan Medical College Tando Adam, Pakistan.

<sup>e</sup> Department of Pharmacology, MMC, Mirpur Khas, Pakistan.

### **Authors' contributions**

*This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.*

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## **ABSTRACT**

**Objective:** To determine the effectiveness of hydroxyurea on the blood transfusion rate in patients with beta-thalassemia major.

**Materials and Methods:** This cross-sectional study was held in the Department of Genetics and Molecular Biology/Pathology at LUMHS Jamshoro, and Diagnostic and Research Laboratory, in Hyderabad, Sindh from February 2015 to August 2015. Patients with beta thalassaemia major, diagnosed with Hb electrophoresis, who had Hb less than 7 g/dl and were regularly transfused every two to four weeks were included. 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. In comparison to those who did not receive hydroxyurea treatment. The ability to keep haemoglobin levels over 9 g/dl or a lowering of at least 50% from the initial transfusion needs were considered signs of therapeutic success. Data was entered and analyzed using SPSS 26.

**Results:** The mean age of the patients was 11.02±3.93 years and males were in the majority (68.0%). In 56.2% of cases, there was a positive family history. The mean serum ferritin level was

<sup>\*</sup>Assistant Professor;

<sup>#</sup>Professor of Hematology & Head;

<sup>†</sup>Resident;

<sup>\*</sup>Corresponding author: E-mail: sumaircool85@yahoo.com;

12824.39±300.60 ng/ml and the mean haemoglobin level was 7.52±1.67 gm/dl. Some 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 most effective treatment to decrease the blood transfusion rate, but patients should be treated under proper and responsible observation.

**Keywords:** *β thalassemia; hydroxyurea; transfusions.*

## 1. INTRODUCTION

β-thalassaemia, the most common genetic blood disorder, is caused by a deficiency in the formation of globin chains, resulting in inadequate erythropoiesis caused by a disparity between the creation of alpha and non-alpha globin chains.[1] Although thalassaemia is common in the individuals from the southern China, Central Asia, Mediterranean, the Middle East and India, it is not any longer unique to these regions due to migration to other parts throughout world.[2,3] Around 5.0 percent of the population of world suffers from haemoglobin-related disorders, and thalassaemia carriers account for about 1.7 %.[4] Thalassaemia affects between 5.0 % and 8.0 % of the Pakistani population, and approximately 5,000 children are born with thalassaemia major each year in Pakistan.[5] Regular blood transfusions are the standard treatment for B-TM, but besides the possibility of the additional risk of transmitting blood-borne diseases, blood transfusions gradually create overload of the iron in key organs such as the heart and liver, which may also lead to early mortality.[4,6] A hallmark feature of thalassaemia is the disproportion in the ratio of α/β-chains, which can be reduced by attempting to compensate for the defective β-chain globin molecule with increased globin-productivity, which ultimately forms HbF, and this onset of HbF limits the need for blood transfusions, as well as iron chelation of the iron, to avoid complications linked to the overload of iron caused by the transfusion therapies.[7,8] As a result, several drugs have been studied to try to decrease the need for transfusions. Hydroxyurea (HU), a fetal Hb inducer that reduces the imbalance of the /globin chain and is predictable to treat chronic anaemia and reduce the requirements of the blood transfusions, is effective.[2,9] Hydroxyurea, which seems to be a ribonucleotide reductase inhibitor, can improve hemolytic symptoms by increasing HbF synthesis and partially rectifying the disparities between non-globin chains and the 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 was done to ascertain the effectiveness of Hydroxyurea in terms of the reduction in the blood transfusion rate among individuals having Beta-thalassaemia major.

## 2. MATERIALS AND METHODS

This cross-sectional study was conducted at the Department of Pathology/Molecular Biology and Genetics, LUMHS Jamshoro, and Diagnostic and Research Laboratory, Hyderabad, Sindh. The duration of the study was six months, from February to August 2015. All patients with beta thalassaemia major, diagnosed with Hb electrophoresis, who had Hb less than 7 g/dl and were regularly transfused every two to four weeks were included. All patients with other haemoglobinopathies and other genetic diseases were excluded. Patients were divided into two groups in equal numbers. Half of the patients underwent blood transfusion with hydroxyurea treatment and half without hydroxyurea. After giving informed consent, hydroxyurea was started in the range of 8–14 mg/kg/day. A fixed haematologist visited the participants every two weeks to assess their clinical and analytical responses. Any signs of new-onset extramedullary haematopoiesis, such as hepatosplenomegaly or facial bone abnormalities, were assessed clinically. A complete blood count (CBC) was analysed for basic haematological parameters using an automated cellular analyzer (Sysmex XN 1000i, Tokyo, Japan). The drug was discontinued if patients developed an intolerance or if their laboratory tests revealed leukopenia, a low platelet count, or abnormal RFTs or LFTs. LFT, haemogram, TFR, and ferritin levels, as well as

height, weight, and liver and spleen size were assessed monthly during this time. Patients' treatment responses and HU side effects were also monitored compared to those who did not receive hydroxyurea treatment. The ability to keep haemoglobin levels over 9 g/dl or a lowering of at least 50% from the initial transfusion needs were considered signs of therapeutic success. All data were collected using a study form. SPSS version 26 was used to analyse the data.

### 3. RESULTS

The mean age of the patients was found to be 11.02±3.93 years, ranging from a minimum of 8 years to a maximum of 20 years. Males were higher than females, at 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 could 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 haemoglobin 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. Patients with (G-C) mutations had a particularly good response to hydroxyurea, as evidenced by a significantly lower blood transfusion rate (p-0.001) Table 3.

### 4. DISCUSSION

In contrast to individuals who do not get hydroxyurea treatment, those with overt clinical manifestations of the disease may be Beta thalassemia homozygotes (Thalassemia major), presenting with severe transfusion-dependent anaemia from around 6 months of life [5]. In our study, the patients' average age 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 and ranging with 1-16 years overall average age was 7.34±3.58 years. On the other hand, Kosaryan et al. [10] also found

**Table 1. Descriptive statistics of the demographic characteristics n=80**

Variables	Statistics
Age (years)	11.02±3.93 years
Gender	Males
	68.0 %
Family history	Females
	32.0 %
Serum Ferritin level	Positive
	45/56.2 %
Haemoglobin level	Negative
	35/43.8 %
	2824.39±300.60 ng/ml
	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	0.001
IVS 1 - 1 (G-T)	04	01	
Fr 8 - 9	01	00	
CD 30 (G-A)	01	01	
Fr - 16 (-C)	01	01	
Fr 41 - 42	01	00	
Del 619	00	01	
CD 5 (-CT)	01	00	

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]. Due to the fact that it binds to and the intracellular iron sequesters, it plays a crucial function in iron homeostasis. Serum ferritin testing is becoming a frequent clinical finding, with elevated concentrations being a common finding. raised in serum ferritin concentrations are associated to with or without overload of iron 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 10 g/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 the cases of  $\beta$  - thalassaemia. 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 patients with thalassaemia 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.

## 5. CONCLUSION

As per the study's conclusion, hydroxyurea was observed to be an effective treatment to decrease the blood transfusion rate, but patients should be treated under responsible and proper observation. Further large-scale studies are advised to evaluate the impact of Hydroxyurea in decreasing the frequency of transfusion amongst individuals with -thalassemia because of the study's limited sample size and single-center approach.

## CONSENT

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

## ETHICAL APPROVAL

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

## COMPETING INTERESTS

Authors have declared that no competing interests exist.

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