Treatment Response to Hydroxyurea in Beta Thalassemia

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Abstract

Introduction: Thalassemias are a group of haematological disorders due to quantitative defect of globin chain. Patients require continuous transfusion support with chelation therapy throughout the life with resultant iron overload and toxic injury to various organs. So there was always a need for a therapy which could substitute for this transfusion therapy. Hydroxyurea (HU) has been proved as one of the accepted agents which acts by combating the imbalance between α and non α chains. We conducted this study at Thalassemia centre Pakistan Institute of Medical Sciences (PIMS) to evaluate response of HU in patients of Thalassemia who were under transfusion management.

Patients & Methods: A prospective study was conducted at Thalassemia Centre of Pakistan Institute of Medical Sciences, Islamabad. Hundred patients of β Thalassemia who were under transfusion management were treated with HU in a dose of 15-20 mg/kg body weight and they were evaluated for about 6 months for clinical and haematological response. Patients were divided into three groups depending upon their response into; good responder, partial responders and non responders.

Results: In total of 100 (89 Thalassemia major and 11] Thalassemia intermedia) 56 were males and 44 were females with age range of 1-16 years (7.34 ± 3.58). Our results showed that 23% of children were good responders, 72 partial responders and 5 were non responders. A significant increase in transfusion interval (p-value 0.000) was found after treatment with HU. There was also a significant reduction in size of liver and spleen (p-value 0.003 and 0.000 respectively).

Conclusion: Treatment of HU has shown promising results in our study. However response to treatment varies among patients and there is a need to identify various factors which affect treatment response.

Key words: Beta-thalassemia, Hydroxyurea, Blood transfusion.

Introduction

Beta-Thalassemias are a heterogeneous group of inherited disorders of haemoglobin synthesis caused by a quantitative deficiency of functional β globin chains.1,2 Patients with overt clinical presentation of the disease may be Beta-Thalassemia homozygotes (Thalassemia major), usually manifesting with severe transfusion dependent anaemia from about 6 months of life. However, about 10% of individuals, despite being homozygotes, have a relatively benign clinical phenotype with survival with or without intermittent blood transfusion, and are known as Thalassemia intermedia. Thalassemia intermedia (TI) is a group of thalassemic patients who are clinically moderately anaemic, maintain a haemoglobin level of 7-10 gm/dl and are usually transfusion independent however typical features of thalassemia as liver and spleen enlargement and typical bone changes are also seen in thalassemia intermedia patients. Individuals with thalassemia intermedia present later in life, have milder anaemia (requiring transfusions not before 2 years and that too infrequently).3

About 5-8% of our population has β Thalassemias trait and over 5000 thalassemia major children are born in Pakistan each year.4 The diagnostic modalities for identification of β thalassemia include complete blood picture, altered erythrocyte morphology, Hb electrophoresis or high performance liquid chromatography (HPLC) and PCR. Most of Thalassemia major patients who are homozygous or compound heterozygous for thalassemia mutations have a severe phenotype of the disease and suffer from chronic anaemia and require regular blood transfusions. The mainstay of treatment is palliation with blood transfusion and iron chelation therapies. Conventional therapeutic management of thalassemia is cumbersome, costly and has side effects.5 Due to limited supply of blood and risk of
transfusion-transmitted viral infections, there was a need to look for alternative approaches to manage beta-thalassemia. Efforts have been undertaken to find out an alternative approach to transfusion in β thalassemia. Since an imbalance in the ratio of α and non-α globin chains is the major pathophysiological mechanism leading to ineffective erythropoiesis and hemolysis in homozygous β-Thalassemia. Hemoglobin F augmentation has been found to be an alternative and safe approach to treat these patients as it can compensate for an imbalance of α chains. Three classes of HbF inducing agents have been introduced. They are hypomethylating agents (such as HU, decitabine and 5-azacytidine), histone deacetylase inhibitors (like sodium phenylbutyrate, and isobutyrate), and recombinant erythropoietin. Most of these agents did not become popular mainly because of toxicity and poor practicability. Hydroxyurea (HU) is the most widely accepted HbF inducer, and its efficacy was investigated in several studies. It is a ribonucleotide reductase inhibitor, capable of increasing HbF production and partially correcting α and non-α globin chains imbalance, thus decreasing the hemolytic symptoms of these patients. HU promotes fetal haemoglobin (HbF) production via a reactivation of γ genes as a result of molecular mechanisms that are not yet clear. The clinical benefit induced by this compound in patients affected with sickle cell disease has been repeatedly demonstrated. A significant benefit could also be expected in patients with β-thalassemia, because the imbalance in globin chains could be improved by the newly synthesized γ chains, which could partially correct ineffective erythropoiesis. HU has been used in Thalassemia major and thalassemia intermedia patients since 1994 and with some degrees of success in different centers. It has a potential to decrease transfusion requirements, extramedullary hematopoiesis and organomegaly. HU also reduces serum ferritin levels. Promising results with clinical and hematologic benefits have been reported with use of HU in different national and international studies. These studies have also reported some increment in Hb level in their patients.

In this study, we planned to evaluate response of HU including reduction in transfusion requirement, increased interval between transfusions and improvement in their clinical and haematological parameters in both β thalassemia major and intermedia patients.

**Patients & Methods**

A prospective study was conducted at Thalassemia centre, Pakistan Institute of Medical Sciences, Islamabad during 2012-2013. About 100 patients of β Thalassemia who were registered at Thalassemia Centre PIMS, Islamabad and were under transfusion management were included in the study. Patients with hypersplenism or other chronic illness (unrelated to Thalassemia) were excluded from the study. Apart from this, patients who become non compliant during the treatment period were also excluded. Clinical features of all the patients including age at first transfusion, frequency of transfusion, liver and spleen size were noted at the start of study. All patients also underwent base line investigations at the start of study, including CBC (complete blood count), LFTs (liver function tests) and serum ferritin. Patients were on transfusion management and were also receiving iron chelation therapy. For iron chelation therapy recommendations of Thalassemia International Federation were followed and chelation therapy was started when patients had received 10-20 transfusions or had serum ferritin level > 1,000 μg/l. Iron chelation therapy was given depending upon their ferritin level and bodyweight either subcutaneously/I/V (Desferal) or orally (Deferiserox or Deferiprone), depending upon the availability. The patients of Thalassemia major and Intermedia were given Hydroxyurea with a starting dose of 15-20mg/kg/day. Dosage was adjusted based on weekly counts.

Eligibility criteria for HU were:

- A diagnosis of Thalassemia major or intermedia on transfusion management
- CBC shows platelets counts greater than 100000 and ANC (Absolute neutrophils count) is greater than 1500

If at any time they showed intolerance or their laboratory tests show leucopenia or decreased platelet count, deranged RFTs or LFTs, the drug was discontinued temporarily and restarted at lower dose and increased again till the desired effect is achieved. Patients were followed for 6 months for the response of treatment. During this period their weight, height, liver and spleen size their CBC, LFT, RFT and ferritin were checked monthly. Patients were also be monitored for treatment response and side effects of HU. Treatment response was defined as the ability to maintain hemoglobin above 9g/dl or reduction of at least 50% of baseline transfusion requirements. According to response to treatment the patients were categorized as /good responders (if they did not require transfusion after treatment or their transfusion interval increased more than 50% of the pre-therapy), partial responders (declined transfusion requirement i.e. less than 20%, or decrease in size of liver and spleen or improvement in well being), poor responders (transfusion requirement not declined). A criterion for giving transfusion was 7gms/dl.

All the data was entered on SPSS version17 for further analysis. Frequencies of various numeric variables were calculated and One-Way ANOVA test was applied to compare various parameters before and after treatment.

**Results**

In total of 100 (89 Thalassemia major and 11 Thalassemia intermedia) 56 were males and 44 were females with age
Clinical and hematological response with HU has been reported in sickle cell disease and Thalassemia intermedia patients but response to treatment in Thalassemia major has been reported in very few national studies. In this study, 23% patients showed a good response to the treatment and 72% showed a partial response i.e. about 95% showed response (partial or complete) to treatment. Ariel Koren reported that 82% of transfusion-dependent patients responded to HU and became transfusion-independent. It has been found that among other factors Xmnl polymorphism is associated with better γ-globin gene reactivation and better response to treatment. It has been reported that Xmnl homozygous patients became transfusion-independent following the HU therapy.

Another study was conducted in Karachi by Saqib et al in which twenty patients of Thalassemia major were evaluated after 24 months of treatment with HU. The mean volume of RC transfused was reduced significantly (p value <0.001) and interval between transfusions was increased by 68.7%.

### Table 1: Clinical and Haematological Parameters Before and After Treatment(n=100)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Pre Therapy Range (Mean ± SD)</th>
<th>Post Therapy Range (Mean ± SD)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Transfusion interval (days)</td>
<td>10-80 (42.85 ± 27.43)</td>
<td>7-1800 (93.29 ± 252.66)</td>
<td>0.000</td>
</tr>
<tr>
<td>Hemoglobin (g/dl)</td>
<td>4.12 (7.56 ± 1.426)</td>
<td>3.4-12.4 (7.85 ± 1.649)</td>
<td>0.102</td>
</tr>
<tr>
<td>Liver enlargement (cm BCM)</td>
<td>0-4 (0.86 ± 1.470)</td>
<td>0-4 (0.61 ± 1.262)</td>
<td>0.003</td>
</tr>
<tr>
<td>Spleen enlargement (cm BCM)</td>
<td>0-4 (0.94 ± 1.530)</td>
<td>0-4 (0.57 ± 1.262)</td>
<td>0.000</td>
</tr>
</tbody>
</table>

p- value of < 0.05 was taken as statistically significant. BCM - below costal margin; 0- not palpable

range of 1-16 years (7.34 ± 3.58). Age at first transfusion ranged from 5 months to 5 years with mean of 7.36 months ± 9.50 SD. A significant increase in transfusion interval (p-value 0.000) was found after treatment with HU. There was also a significant reduction in size of liver and spleen (p-value 0.003 and 0.000 respectively). Their hemoglobin also increased after treatment though this rise was not statistically significant (p-value 0.102). Table1.

Our results also showed that 23% of children were good responders, 72 partial responders and 5 were non responders. (Table 3) We divided the patients into 2 groups depending upon their ferritin levels. Group 1 with ferritin level less than 2000 and Group 2 with ferritin level more than 2000. Comparison of effects of treatment in two groups showed A significant increase in transfusion interval in group 1 (p-value 0.000), decrease in spleen size (p-value 0.000) and rise in Hemoglobin (p-value 0.040) was found in Group 1.

### Discussion

Beta Thalassemia is our most prevalent hereditary blood disorder, resulting from defective synthesis of β-globin chain which leads to ineffective erythropoiesis and requires regular blood transfusion, as well as iron chelation therapy. Increase in fetal Hb by HbF augmenting agents which neutralizes the excess alpha-globin chains in red cells leads to longer red cell life span and thus improvement in clinical and hematological improvement. This is manifested by increased transfusion intervals and decreased volume of red cell transfusions. The use of HU has shown promising clinical and hematological benefit in these patients; however response to hydroxyurea varies among patients. 3

Clinical and hematological response with HU was reported in sickle cell disease and Thalassemia intermedia patients but response to treatment in Thalassemia major has been reported in very few national studies. In this study, 23% patients showed a good response to the treatment and 72% showed a partial response i.e. about 95% showed response (partial or complete) to treatment. Ariel Koren reported that 82% of transfusion-dependent patients responded to HU and became transfusion-independent. It has been found that among other factors Xmnl polymorphism is associated with better γ-globin gene reactivation and better response to treatment. It has been reported that Xmnl homozygous patients became transfusion-independent following the HU therapy. Another study was conducted in Karachi by Saqib et al in which twenty patients of Thalassemia major were evaluated after 24 months of treatment with HU. The mean volume of RC transfused was reduced significantly (p value <0.001) and interval between transfusions was increased by 68.7%.
In another study conducted by them in 2011 to look for efficacy of HU in providing transfusion independence in β-Thalassemia they found that 41% did not require any transfusion after using HU, 39% showed partial response with greater than 50% reduction in RC transfusion. The mean volume of RC transfused was reduced for all patients with a significant increase in transfusion interval, decrease in spleen size and reduced ferritin levels. They also reported improved well being of children receiving HU, increased exercise tolerance, increased appetite, weight gain and healthy psychosocial effect on children.12

Alebouyeh et al found similar response, and his patients exhibited a rise in post-HU treatment Hb, as well as a decrease in serum ferritin.13 We also observed that patients who had ferritin levels less than 2000 ng/ml showed better response to treatment with significantly increased transfusion interval and significant reduction in size of liver and spleen as compared to patients who had ferritin levels more than 2000 ng/ml.

We started with a dose of HU 15-20 mg/kg. The duration of treatment does not affect the response rate, so if HU therapy does not lead to a satisfactory response after treatment with optimal doses for about 3-6 months, its beneficial effects in a patient should be analyzed. In a study done in Iran on 297 patients an excellent response was reported in 44.7% of thalassemia major patients with the mean Hb of 10g/dl. The remaining patients needed transfusions less frequently than before treatment with HU. The changes in Hb and HCT before and after HU were also statistically significant in their study (p <0.001).14

In our study hemoglobin level was increased after treatment with HU though this rise was not statistically significant. Our results are comparable with another study conducted in Iran which showed a good clinical response in their patients though there was not a significant increase in hemoglobin.15,16 HU also plays an important role in suppressing extramedullary haematopoiesis and thus reduces skeletal abnormalities and has also an effect in reducing liver and spleen size. We found a significant reduction in size of liver and spleen (p value 0.003 &0.000 respectively) after treatment with HU. Saxon B.R. et al reported a case of thalassemia in which they observed its effect on Hb and extramedullary hematopoiesis. They reported that there was not only an increase in hemoglobin but an appreciable regression of extramedullary hematopoiesis as shown by MRI studies and reduction in bone pains.17 Another study was conducted by Bradai M et al reporting clinical and hematologic improvement with HU and regression of extramedullary hematopoietic masses in patients with β Thalassemia. They also reported that a reduction in extramedullary hematopoiesis has resulted in decrease in size of spleen and decreased number of circulating erythroblasts.18 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

Conclusion

Treatment of HU has shown promising results in our study with good response in 23% and partial response in 72% patients. However response to treatment varies among patients; it is therefore suggested to identify various factors which affect treatment response. Moreover molecular understanding will unveil further aspects of these entities as well as give new vistas in their management.

References

15. Yavarian M, Karimi M, Bakker E, Harteveld CL, Giordano PC. Response to hydroxyurea treatment in Iranian
transfusion-dependent beta-Thalassemia patients. Haematologica. 2004;89(10):1172-8