

# Hydroxyurea Can Reduce or Eliminate Transfusion Requirements in Children with Major and Intermediate Thalassemia

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## Abstract

**Background:** Hydroxyurea (HU) is a well known chemotherapeutic agent that has been used largely for various myeloproliferative diseases over the past 20 years. In  $\beta$ -thalassemia, the effect of HU is much less clear and remains controversial. This study was undertaken to describe the hematologic and clinical responses of thalassemia major and intermediate patients to HU treatment during 2 years.

**Materials and Methods:** Seventy one major and twenty transfusion-dependent intermediate thalassemia participants were selected among 150  $\beta$ -thalassemia patients. All patients underwent laboratory tests, and the state of energy, social activity, tolerance, and mood were recorded in the beginning of the study. Echocardiography was carried out before and during treatment with HU. All patients were treated with HU; the initial dose was 10-15mg/kg/day given once a day.

**Results:** All the patients tolerated HU well and showed a dramatic response to the drug. Nine of 20 intermediate and 8 of 71 major patients became completely transfusion free. In 6 intermediate and 15 major patients, transfusion interval prolonged more than 50%. After treatment, 95% of intermediate and 81% of major patients described an increase in social activity. HU therapy was also associated with a marked decrease in serum ferritin level in major thalassemia patients.

**Conclusion:** HU may be administered in thalassemia major and intermediate patients to minimize or obviate the need for regular transfusion and concomitant iron overload. HU therapy appears to be safe and effective when administered in thalassemia patients.

**Keywords:** Hydroxyurea, Thalassemia, Transfusion.

## Introduction

Major  $\beta$ -thalassemia is an inherited hemoglobinopathy. It is one of the most common hemoglobinopathies in Asia and Iran.<sup>1</sup> About 3% of the world population and 5% of Iranian people are  $\beta$ -thalassemia carriers. In Iran, there are about 20000 patients suffering from major  $\beta$ -thalassemia.<sup>1</sup>

There is some evidence that Hydroxyurea (HU) can increase gamma-globin, and can be a therapeutic agent for  $\beta$ -thalassemia patients.<sup>2</sup> Clinical and hematological improvement have been also reported in patients with thalassemia intermedia,<sup>3-8</sup> but efficacy in patients with thalassemia major is controversial.<sup>5,9</sup> We followed 91 patients with

transfusion dependent  $\beta$ -thalassemia (71 major thalassemia and 20 intermediate thalassemia) and treated them with hydroxyurea to evaluate if it could reduce transfusion needs.

## Materials and Methods

Among 150  $\beta$ -thalassemia patients, 91 patients (71 major thalassemia and 20 transfusion-dependent intermediate thalassemia subjects) were selected in Yazd between 2005 and 2007. Criteria for thalassemia intermedia were need for transfusion after the age of 2 years old and/or hemoglobin (Hb) level of 7 mg/dl or more. The patients included 48 males and 43 females with an age range of 3 to 40 years old (average 16.5 years).

Our criteria for starting blood transfusion after the age of 2 years old were based on two factors: 1) laboratory assessment demonstrating a hemoglobin level below 8 mg/dl resulted in blood transfusion, and 2) clinical findings such as inadequate growth, progressive skeletal deformity, headache, fatigue, congestive heart failure, pathologic fractures and extramedullary hematopoiesis.

Informed consent was obtained from all patients or parents. Medical history was taken and physical examination was performed. All patients were followed by the authors over 6 months. Facial changes, head circumference and length were measured. The state of energy, fatigability, social activity tolerance, and mood were recorded at the beginning and end of the study. Laboratory data including complete blood count (CBC), liver function tests (LFT), serum electrolytes, creatinine (Cr), serum ferritin, HBsAg, HBsAb, and HCV Ab were recorded as baseline and during follow up period. Echocardiography was carried out before and after treatment with HU. A dose of 10-15 mg/kg/day HU was given orally once a day. If hematological toxicity (decrease of absolute neutrophil count, reticulocyte count, or platelet count), hepatic (increase in liver enzymes), or renal toxicity (increase in Cr) occurred, treatment would be stopped. Serum ferritin level was determined at 3-month intervals. Statistical methods included paired student t-test, Wilcoxon test, and chi-square test.

## Results

All of the 91 patients tolerated HU well. A dramatic response to the drug was observed in 76.7% of intermediate patients and 31.9% of major patients.

In intermediate thalassemia group, 9 patients (46%) became completely transfusion free. Transfusion interval in 6 patients (30.7%) increased more than 50%. Mean monthly transfusion volume decreased (192 cc versus 458 cc) ( $P$ -value=0.001), mean serum ferritin level decreased from 2121 to 1293 mg/dl ( $P$ -value =0.052), mean hemoglobin level increased from 8.9 to 9 g/dl ( $P$ -value=0.796 ), mean red blood cell (RBC) count increased from 3.54 to 3.64 million/dl ( $P$ -value=0.56 ), mean corpuscular volume (MCV) decreased from 78.6 to 77.2 fl ( $P$ -value=0.325), mean corpuscular hemoglobin (MCH) decreased from 25.19 to 25.9 pg

( $P$ -value=0.083), and mean cardiac ejection fraction increased from 63% to 65% ( $P$ -value=0.563). Social activity tolerance, and sense of well being increased compared to the beginning of the study ( $P$ -value=0.05).

In thalassemia major group (71 patients ), 7 patients (10.6%) became completely transfusion free, transfusion interval in 15 (21.3%) patients increased more than 50%, mean monthly transfusion volume decreased from 572 cc to 442cc ( $P$ -value=0.001), mean serum ferritin level decreased from 2557 to 1981 mg/dl ( $P$ -value<0.05), mean hemoglobin level decreased from 9.47 to 8.64 g/dl ( $P$ -value<0.05), mean RBC count decreased from 3.44 to 3.24 million/dl ( $P$ -value=0.015), MCV decreased from 83.2 to 82.3 fl ( $P$ -value=0.152), MCH decreased insignificantly from 27.12 to 26.74 pg ( $P$ -value=0.092), mean cardiac ejection fraction decreased from 62.53% to 58.9% ( $P$ -value=0.008), social activity tolerance and sense of well being increased compared to the beginning of the study ( $P$ -value<0.05).

Side effects of HU including abdominal pain, fatigue, anorexia, chest pain, nausea, vomiting, leucopenia, thrombocytopenia, hemoglobin level decrease, and raise of liver enzymes occurred in 7 (10.6%) major and 6 (30%) intermediate thalassemia patients. However, adverse reactions were resolved after a short term of discontinuing HU.

## Discussion

$\beta$ -thalassemia is a common genetic disorder and also an important public health problem in many countries. HU is a well known cytostatic agent. Introduced 20 years ago for the treatment of myeloproliferative diseases, it remains an easy-to-handle medication due to reversibility of its toxicity.<sup>10</sup> HU is an effective agent to raise HbF and Hb level.<sup>11,12</sup>

Although HU increases fetal Hb levels in patients with sickle cell disease,<sup>13</sup> there is limited experience with HU in thalassemia, particularly in a large group of major thalassemia patients. To the best of our knowledge, this is the first study evaluating HU given alone in a large sample size of major thalassemia patients.

In our study, HU was easy to use and well tolerated in all patients. Toxicity was not

considerable even at maximal doses (10-15 mg/kg). Moreover, in the rare instances of leucopenia or thrombocytopenia temporary discontinuation of the drug resulted in rapid normalization of the cell count and allowed resumption of therapy. Our results showed alleviation of clinical symptoms such as loss of energy, fatigue, and depression after HU therapy, which could be explained by the increased transfusion intervals.

These findings are similar to those reported by others who showed an increase in transfusion intervals in thalassemia and marked improvement in clinical findings.<sup>10,14-19</sup> Increase in energy, social activity tolerance, and sense of well being was observed in 81% of thalassemia major patients and 95% of thalassemia intermediate patients in our study. In this study, 9 (45%) intermediate patients and 7 (9.8%) major patients became completely and rapidly transfusion free after HU therapy. This is in concordance with several previous studies.<sup>14,16-19</sup> However, the only study on major thalassemia patients was reported by Bradai et al.<sup>16</sup> In our study, transfusion interval in 6 intermediate patients and 15 major patients increased more than 50%.

Rare instances of side effects were managed by temporary discontinuation of the drug. This finding has been reported in previous studies.<sup>14,16,20</sup> Possible influences of undetermined factors on the pharmacodynamics and pharmacokinetics of the drug should be of great importance in side effects occurrence. The heterogeneous nature of the disease resulting from different mutations and its effect on the response to HU must also be considered.

In this study, mean monthly transfusion volume decreased in both groups (major and intermediate) ( $P$ -value<0.05). Decrease in transfusion volume has been reported by Cario et al.<sup>10</sup> Our results showed a significant decrease in mean hemoglobin level in thalassemia major patients and an insignificant raise in mean hemoglobin level in thalassemia intermediate patients. Previous reports have reported a raise in Hb.<sup>14,16,17,22</sup> However, most of them have evaluated thalassemia intermediate patients. Moreover, Hb level of our patients was over 8-9 g/dl before starting HU therapy.

Our results showed a significant decrease in ferritin level in major thalassemia patients ( $P$ -

value<0.05), and an insignificant decrease in intermediate patients ( $P$ -value=0.052). This decrease has been reported by Alebuyeh et al.<sup>17</sup> Decrease in ferritin level could be explained by transfusion volume decrease. There was no significant difference in MCV and MCH after HU treatment. Alteration in MCV index has been reported by Karimi et al.<sup>14</sup> in intermediate patients. Increase in MCV has been reported by Zeng et al.<sup>3</sup>, Vinicius et al.<sup>22</sup>, and Bradai et al.<sup>16</sup>. Our result showed a decrease in mean red blood cell count in major thalassemia patients, this decrease in mean red blood cell count has been reported by Loukopolus et al.<sup>6</sup>

There were significant differences in mean red blood cell count in intermediate patients and no significant differences in MCH in both groups. Zeng et al.<sup>3</sup> and Loukopolus et al.<sup>6</sup> have reported an increase in MCH index, but Karimi et al.<sup>14</sup> has reported a decrease in MCH value in intermediate patients. This difference could be related to the effect of HU on the emergence of erythroid progenitors.

Our result showed a decrease in left heart ejection fraction in major thalassemia patients but no difference in intermediate patients. Rashidighader et al.<sup>23</sup> has reported that HU therapy did not affect EF in 60 intermediate patients. It is unclear that decrease of EF in our study is because of HU therapy or a component of thalassemia natural history.

Genetic analysis for thalassemia seems to be necessary to help us clarify the reasons for failure of HU therapy. Other factors such as erythropoietin level or metabolic changes should also be considered. We found a good response in 77% of thalassemia intermediate and 32% of thalassemia major patients.

## Conclusion

We suggest using HU in thalassemia major and intermediate patients to minimize or even obviate the need for regular transfusion, and concomitant iron overload during therapy. Our data suggests that HU therapy is safe and effective in treatment of extramedullary hematopoiesis complications in thalassemia patients.

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