Hydroxyurea Therapy in 49 Patients with Major Beta-Thalassemia

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Major thalassemia is one of the most common hemoglobinopathies in many Asian countries including Iran. Pharmacologic agents such as hydroxyurea have been known to enhance the production of fetal hemoglobin, and also an increase in total hemoglobin level has been repeatedly reported during hydroxyurea treatment in patients with sickle cell disease and in several patients with intermediate beta-thalassemia. We evaluated the long-term efficacy and safety of hydroxyurea in major beta-thalassemic patients.

Forty-nine beta-thalassemic patients enrolled in the study. The mean follow-up time was 60 months. The mean dose of hydroxyurea was 10 mg/kg per day (8 – 15 mg/kg). Before starting hydroxyurea, all patients underwent routine biochemical laboratory tests. Patients with low platelet count (<100,000/mm³), neutropenia (polymorphonuclear neutrophil<1,200/mm³), pregnancy, and on interferon treatment were excluded.

Twenty-eight out of 49 enrolled patients were females with the mean age of 18.38 years (10 – 40 years). The mean packed red cell transfusions during one year before starting of hydroxyurea was 22.75 units which decreased to 6.02 units after treatment (P<0.01). The mean ferritin level during the first period was 2751.44 ng/mL, but decreased to 1594.20 ng/mL after one year of hydroxyurea therapy (P<0.001).

We observed a substantial and persistent increase in hemoglobin level and a significant decrease in blood transfusion. Hydroxyurea treatment was well-tolerated and it did not cause any hematopoietic suppression except in one patient who developed transient thrombocytopenia which resolved after short period of hydroxyurea cessation. We did not encounter any malignancies including leukemia in the five-year follow-up.

Keywords: Hydroxyurea • Iran • major beta-thalassemia

Introduction

Beta-thalassemia is an inherited blood disorder that occurs when a person is unable to produce adequate levels of hemoglobin, the oxygen-carrying component of red blood cells (RBCs). This genetic disorder probably arose about 6,000 years ago as a partial defense against malaria.

This disease is more prevalent in areas of the world named as thalassemic belt. Iran is one of the high-prevalent areas. It is estimated that 3% of the world population and 5% of the Iranian population are beta (β)-thalassemia gene carriers. The most prevalent form of thalassemia in Iran is β-thalassemia. More than 20,000 patients suffer from major thalassemia in Iran.

β-thalassemia major (Cooley's anemia) is the most severe form of β-thalassemia, requiring regular blood transfusions and extensive ongoing medical care. Patients with major β-thalassemia require RBC transfusions every two to three weeks, which means 52 units of blood a year. These lifelong blood transfusions can lead to iron overload, which ultimately damages tissues in the liver, heart, endocrine organs, and joints. Regarding the complications of blood transfusion and limitation of blood supply, the treatment requirements of these patients are justified.
β-thalassemia is a disease resulting from a decrease in β-globin production and a subsequent imbalance in α/β-globin chain ratio. Excess α-chain is precipitated within RBC, resulting in hemolysis and ineffective erythropoiesis. Enhancing γ-globin chain synthesis within RBC reduces α/β-globin chain imbalance and can potentially lead to an improvement in RBC survival and lessens anemia. From the increase of potentially lead to an improvement in RBC increases hydroxyurea (HU) is a pharmacologic agent that reduces ferritin, TIBC, serum iron, ALT, AST, bilirubin, alkaline phosphatase, and uric acid were measured at four-month intervals. Hematologic toxicities were defined by a two-fold increase in ALT or AST (if other cause of hepatitis was not present) or a >50% increase in creatinin level. In case of toxicity, HU therapy was stopped transiently and restarted if normal value achieved. Before study, all patients were splenectomized. The mean dose of HU was 10±5 mg/kg per day (range: 8 – 15 mg/kg). In the absence of side effects, the dose was increased gradually. According to the children’s weight gain we raised the dose of HU. The mean follow-up period was 60 months. Statistical analysis was performed using SPSS software version 15 and t-test for comparison of the means of quantitative variables.

**Results**

Forty-nine patients (28 women and 21 men) enrolled in the study. The mean age of the patients was 18.38 years (range: 10 – 40 years). The mean packed red cell transfusions in one year before starting of HU was 22.75 units, which decreased to 6.02 after treatment (P< 0.01, t-test). The mean Hb levels was 8.52 g/dL and 8.45 g/dL during one year before and after HU therapy, respectively; this difference was not significant (P=0.543, t-test). Before initiation of HU, the patients required blood transfusion every three to four weeks, but only three to four months after treatment, transfusion stopped in 12 patients, spaced out in 32 patients (once every three to four months instead of once every month), and continued in five patients. The mean ferritin level during one year before the starting of HU was 2751.44 ng/mL, but decreased to 1594.20 ng/mL after one year of HU therapy (P<0.001, t-test). The mean deferoxamine injection decreased from 84.83 to 49.46 (P<0.001, t-test) (Table 1). We had only one hematologic complication (platelet<100,000/mm³). Thrombocytopenia was transient, which resolved with discretion of HU dose. Eight patients suffered from
nausea at the beginning of treatment, which resolved spontaneously. There were no hepatic, renal, or other complications during the treatment.

Discussion

The mainstay of treatment in major β-thalassemia still relies on regular blood transfusions and the use of iron chelators. Pharmacologic reactivation of γ-globin genes holds great promise for the treatment of thalassemia syndromes as well as of sickle cell disease. Hydroxyurea has been demonstrated to up regulate γ-chain synthesis and HbF production. This drug has been used successfully in the treatment of sickle cell anemia by increasing HbF levels and reducing clinical complications, although there is limited experience with this agent in betathalassemic patients.9,10

We described the results of the treatment of 49 splenectomized, transfusion-dependent major beta-thalassemic patients with HU. The effects on total Hb, transfusion requirements, and the level of ferritin were the most significant observation of this study.

We observed a significant decrease in blood transfusion. The response to HU was equal in males and females. Decrease of transfusion requirement began in the first three to four months of HU therapy. Our findings show that the effects of HU therapy can occur after a short period of time.

The significant decrease of serum ferritin in the responder group is clinically very important as iron overload is the main hazard to these patients. The serum ferritin decrement is due to decrease of blood transfusion and to a lesser extent due to increased iron utilization by increased Hb production and also suppression of ineffective erythropoiesis.

HU treatment was well-tolerated and it did not cause any hematologic toxicity except in one patient who developed transient thrombocytopenia which resolved after a short period of HU cessation.

Although the carcinogenic effect of long-term use of HU remains a matter of serious concern, we did not encounter any malignancies including leukemia in the five-year follow-up. This study shows that HU can be an effective and safe treatment for major thalassemia in long-term therapy.

References