Efficacy of Hydroxyurea in Thalassemia major patients.

Dr. Jitendra Kumar Jain
M.D., Assistant Professor Pediatrics, Department of Pediatrics, Government Medical College and J.K. Lon Hospital Kota, Rajasthan.

Dr. Sunil Kumar Dadich
M.D., Assistant Professor Pediatrics, Department of Pediatrics, Government Medical College and J.K. Lon Hospital Kota, Rajasthan.

ABSTRACT

Objective: To determine the efficacy hydroxyurea in Thalassemia major patients.

Design: Cross Sectional Study.

Method: Oral hydroxyurea was given to all 60 patients of Beta-thalassemia major with dose of 8-15 mg/kg/day. They have been followed up for a period of 6 months. The age of the patients ranged from 2-16 years (mean age 8.6 yrs) and the mean age of presentation with anemia was 1.68 yr. There was 37 male and 23 female. Response was evaluated with the help of lab evaluation of a rise in hemoglobin and Hbf levels and decreasing serum ferritin and transfusion requirement. Pre HU and post HU group were made for comparing the parameters after HU therapy. HU therapy was stopped transiently if hepatotoxicity and Myelotoxicity appear. Clinically the response was categorized as, good ( Rise in hemoglobin >2 g/dl), partial (Rise in hemoglobin 1–2 g/dl) and non responders.

Results: It was seen that 13/60 (21.66%) had a good response, 18/60 (21%) had a partial response and 23/60 (38.34%) had no response. 6/60 (10%) could not be evaluated, as they dropped out due to various reasons. The mean spleen size decreased significantly (P<0.001), mean monthly transfusion volume decreased significantly (P<0.02), mean Hb level increased significantly (P<0.001), mean Hb-F level increased significantly (P<0.05) and serum ferritin level decreased significantly (P<0.01) in good responders. The mean monthly transfusion volume decreased significantly (P<0.05), mean Hb level increased significantly (P<0.001), mean Hb-F level increased significantly (P<0.05) and serum ferritin level decreased significantly (P<0.05) in partial responders. In mean spleen size decreased but did not reach to significant level (P>0.1) in non responders.

Conclusion: Hydroxyurea can be used in thalassemia Major patients to decrease the need for regular transfusion and concomitant iron load.

Introduction: B-thalassemia major 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. These cases need regular blood transfusion and iron chelation. γ-globin chain enhancement in RBC can potentially lead to an improvement in RBC survival and lessen anemia by reducing α/β-globin chain imbalance. It has been observed that (HU) is a pharmacologic agent that increases γ-globin production.1,2

Patients and Methods: Sixty thalassemia major patients attending the Regional Institute of Mother and Child Health Centre Umaid Hospital, Jodhpur, from July 2011 to December 2011 were enrolled for the study. Written informed consent was obtained before the enrollment. Diagnosis of thalassemia was based on quantification of Hbf and HbA2 by high performance liquid chromatography, clinical presentation and blood transfusion requirement in first six months of life and requirement of blood transfusion one to two times in a month before starting hydroxyurea. Cases with pre existing renal or hepatic diseases were excluded. Hepatic disease and toxicity was defined when serum Creatinin value is >50% of its normal value which shall be taken as 0.5-1mg/dl. Hemolytic facies were present in 80% of cases and all patients had organomegaly with mean palpable liver size of 3.74±1.18cm and mean palpable spleen size of 5.66±1.66cm. Blood transfusion requirement was two to three times in a month before starting Hydroxyurea Laboratory data including complete blood count (Autoanalyzer), liver function test (LFT), blood urea, serum creatinine, blood sugar level, serum calcium, serum ferritin (done by chemiluminescence, CLIA Kits), HBsAg, HCV, HIV status and HPLC (Bio-Rad Variant) for Hb variants were recorded. S. ferritin value would be measured before starting HU therapy. Baseline Hb was calculated prior to start HU therapy in each case which was average of pre transfusion Hb of last six months. Similarly average blood transfusion requirement of last six months was calculated prior to start HU therapy. Duration of follow up was of 6 months. All patients were treated with folate and calcium supplements during HU therapy. In every 4 weekly, we advised complete Hemogram, blood urea, creatinin and liver function during follow up. We also observed clinical side effects and compliance with dosing during follow up. S. ferritin and Hb-F level were estimated at the end of the study. Myelotoxicity was defined by absolute neutrophil count (ANC) less than 1.5×10^9/l or platelet count less than 100×10^9/l. HU therapy was stopped transiently and restarted if normal value of lab parameters achieved. HU was used in a dose of 8-15 mg/kg/day. Starting dose of HU was 8 mg/kg/day which was increased gradually up to 15 mg/kg/day in absence of side effect. Pre HU and post HU group were made for comparing the parameters after starting HU therapy. Clinically the response was categorized in good if baseline hemoglobin increased >2 g/dl, partial when hemoglobin increased 1–2 g/dl and no response when no increment in hemoglobin after HU therapy.

Results: Out of 60 cases 37(61.66%) were male and 23(38.34%) were female with the male to female ratio being 1.61. The mean age of patients was 8.6 yrs (range: 2-18yrs). Majority of cases (46.67%) were in age group of 6-10yr. The mean age of presentation of our cases with anemia was 1.68yrs. 31 patients (51.66%) showed response to HU therapy. Thirteen patients (45.9%) showed good response, and eighteen patients (30%) showed partial response. Table: 1 shows the comparative parameters for the various variables in partial responders. In good responder mean spleen size decreased significantly (P<0.001), mean monthly transfusion volume decreased significantly (P<0.02), mean Hb level increased significantly (P<0.001), mean Hb-F level increased significantly (P<0.05) and serum ferritin level decreased significantly (P<0.05). Table: 2 shows the comparative parameters for the various variables in partial responders: In partial responders: mean spleen size decreased but not reach to significant level (P>0.1), mean monthly transfusion volume decreased significantly (P<0.05), mean Hb level increased significantly (P<0.001), mean Hb-F level increased significantly (P<0.05) and serum ferritin level decreased significantly (P<0.05). Most common adverse effect of HU was related to GIT (16%) followed by hepatic (5%) and hematological (1%).
Discussion:

β-thalassemia is a common genetic disorder and also an important public health problem in many countries. HU is a well known cytostatic agent. It used in treatment of myeloproliferative diseases. HU is an effective agent to raise HbF and Hb level. Although HU increases fetal Hb levels in patients with sickle cell disease, there is limited experience with HU in thalassemia, particularly in a large group of major thalassemia patients. In this study we describe the effect of Hydroxyurea in sixty Thalassemic major children. In our study, HU was well tolerated in most of patients, except in the few instances of leucopenia or raised liver enzyme for which temporary discontinuation of the drug, resulted in rapid normalization of the lab parameters and allowed resumption of therapy. Our results showed decrease of extramedullary hematopoiesis after HU therapy, which could be explained by the regression in spleen size. Similar results were observed in other previous studies. Mohamed et al. In this study, mean monthly transfusion volume decreased. Decrease in transfusion volume has been reported by Seyed et al. Our results showed a significant increase in mean total hemoglobin level and Hb-F. Previous reports have reported a raise in Hb and Hb-F level. However most of them have evaluated thalassemia intermedia patients. Our results showed a significant decrease in ferritin level. This decrease has been reported by Alabeouyeh et al and Azamsadat et al. The serum ferritin level is increased 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. Few instances of side effects were managed by temporary discontinuation of the drug. This finding has been reported in previous studies.

Conclusion:

We suggest that use of Hydroxyurea can decrease the need of regular blood transfusion and iron overload in thalassemia major patients. Our data suggests that Hydroxyurea therapy is safe and effective in thalassemia major patients.

Conflict of interest: -Nil.

Funding: -Nil.

References:

Table: 1 shows the comparative parameters for the various variables in good responder before and after therapy.

<table>
<thead>
<tr>
<th>S. No.</th>
<th>Parameters</th>
<th>Pre Hu Group(N=18)</th>
<th>Post Hu Group(N=13)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>Spleen size(cm) Mean±SD</td>
<td>3.84±0.89</td>
<td>3.84±0.89</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>2.</td>
<td>Hb (g/dl) Mean±SD</td>
<td>8.62±0.45</td>
<td>8.62±0.45</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>3.</td>
<td>Hb-F Mean±SD</td>
<td>7.32±10.07</td>
<td>7.32±10.07</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>4.</td>
<td>S.ferritin(ng/ml) Mean±SD</td>
<td>4.23</td>
<td>2654.62±114.42</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>5.</td>
<td>Average blood requirement (ml/month) Mean±SD</td>
<td>3.96±2.66</td>
<td>6.89±1.08</td>
<td>&lt;0.05</td>
</tr>
</tbody>
</table>

Table: 2 shows the comparative parameters for the various variables in partial responders before and after therapy.

<table>
<thead>
<tr>
<th>S. No.</th>
<th>Parameters</th>
<th>Pre Hu Group(N=18)</th>
<th>Post Hu Group(N=18)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>Spleen size(cm) Mean±SD</td>
<td>5.56±1.89</td>
<td>4.81±1.51</td>
<td>&gt;0.1</td>
</tr>
<tr>
<td>2.</td>
<td>Hb (g/dl) Mean±SD</td>
<td>7.99±1.09</td>
<td>9.37±11.45</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>3.</td>
<td>Hb-F Mean±SD</td>
<td>9.60±1740.96</td>
<td>2654.28±165.03</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>4.</td>
<td>S.ferritin(ng/ml) Mean±SD</td>
<td>35.67±112.16</td>
<td>1.36±0.49</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>5.</td>
<td>Average blood requirement (ml/month) Mean±SD</td>
<td>402.61±137.0</td>
<td>335.61±137.8</td>
<td>&lt;0.05</td>
</tr>
</tbody>
</table>