Asian Journal of Clinical Pediatrics and Neonatology Original Article

# Efficacy of hydroxyurea in Thalassemia major patients

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## Abstract

**Background:** Purpose of this study was to determine the efficacy of hydroxyurea in Thalassemia major patients. Non-randomized, interventional, prospective single centre study. **Methods:** Hydroxyurea (HU) was administered orally to Beta-thalassemia major patients in doses of 8-15mg/kg/day. They were followed up for a period of 6 months. Before starting hydroxyurea, all patients underwent routine biochemical laboratory tests. Response was evaluated by observing the children for a rise in haemoglobin and Hb F levels and decreasing serum ferritin and transfusion requirement. Pre-HU and post-HU groups were made to compare the parameters after HU therapy. Treatment was stopped transiently if features of hepato-toxicity and myelo-toxicity appear. Clinically, the response was categorized as - good if mean haemoglobin increased >2 g/dl, partial when haemoglobin increased by 1–2 g/dl and the rest were categorized into non- responder group. **Results:** Total 60 patients were recruited with age range of 2-16 years (mean age 8.6 years) and the mean age of presentation with anaemia was 1.68 years. It was observed that 13/60 (21.66%) had a good response, 18/60 (30%) had a partial response and 23/60 (38.34%) had no response while 6/60 (10%) could not be evaluated, as they dropped out. 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 mean serum ferritin level decreased significantly ($P<0.01$) in good responders. Better response was seen with higher dosage regime of the drug. **Conclusion:** Hydroxyurea has a definite role in the overall management of patients with Thalassemia Major to decrease the need for regular transfusions and concomitant iron load.

**Key words** Thalassemia major, Hydroxyurea, Hb-F induction

## INTRODUCTION

β-thalassemia major is a disease resulting from decrease in β-globin production and subsequent imbalance in α/β-globin chain ratio. Excess α-chain is precipitated within the RBCs, resulting in hemolysis and ineffective erythropoiesis. These cases need regular blood transfusion and iron chelation. Gamma-globin chain enhancement in RBC can potentially lead to an improvement in RBC survival and lessen anaemia by reducing α/β globin chain imbalance. It has been known that Hydroxyurea is pharmacologic agent that increases γ-globin production.[1,2] Also, patients who have some genetic mutations leading to Hereditary Persistence of Fetal Haemoglobin (HPFH) or high levels of HbF, have a milder phenotype of the disease.[3-4] The study was based on the observation by various workers that use of drugs that increase the levels of HbF, indirectly help thalassemic patients by modifying the clinical course of the disease. Hydroxyurea is a urea analogue that is safe and has been used successfully by various authors in past.[5-7] Therefore, we planned this study to assess the efficacy and safety profile of hydroxyurea in patients with thalassemia major.

## MATERIAL AND METHODS

Thalassemia major patients attending the thalassemia day care centre at Umaid Hospital, Jodhpur, from July 2011 to December 2011 were included in the study. Written informed consent was obtained before the enrolment. Diagnosis of thalassemia was based on quantification of HbF and HbA2 by high performance liquid chromatography (HPLC), clinical presentation and blood transfusion requirement in the first year of life and a history of blood transfusion one to two times in a month.

Cases with pre-existing renal or hepatic diseases were excluded. Hepatic disease and toxicity was defined when there is more than two fold rise of alanine aminotransferase or aspartate aminotransferase from their normal values. Renal disease and toxicity was defined when serum Creatinine value was >50% above its normal value which was taken as 0.5-1mg/dl.

Laboratory Parameters Evaluated:- Complete blood count (by Auto analyser), liver function tests (LFT), blood urea, serum creatinine, blood sugar levels, serum calcium, serum ferritin (by Chemiluminescence, CLIA Kits), HBsAg, HCV and HIV were performed in each case. HPLC (Bio-Rad Variant) was used for recording the levels of the Hb variants. Serum ferritin values were measured before starting HU therapy. Baseline Hb was calculated prior to starting 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 starting HU therapy.

Intervention: HU was used in a dose range of 8-15mg/kg/day. Starting dose of HU was 8 mg/kg/day which was increased gradually in increments of 2-3mg/kg every 4 weeks till a maximum of 15mg/kg was reached with no side effects. This incremental dosing was done only in the first 12 weeks of therapy. The dose selected was based on the study by Hoppe et al, who showed that a good and prolonged response was achieved with low doses of HU (3-10mg/kg/day) and higher doses were associated with mild reversible haematological toxicity and no further increase in Hb.[5]

End Point Variables: Clinically, the response was categorized as good if rise in haemoglobin was >2 g/dl, partial when rise was between 1 and 2 g/dl and no response when no

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increment in haemoglobin was seen after HU therapy.

Follow Up: Duration of follow up was 6 months. All patients were treated with folate and calcium supplements during HU therapy. During every 4 weekly follow-up visits, complete hemogram, blood urea, creatinine and liver function tests were done. Any clinical side effects and compliance with dosing during follow up was recorded. Serum ferritin and Hb-F levels were estimated at the end of the study. Myelotoxicity was defined by absolute neutrophil count (ANC) less than 1.5×109/l or platelet count less than 100×109/l and at these values HU therapy was stopped transiently and restarted if normal values of lab parameters achieved. Pre-HU and post-HU group were made to compare the parameters after HU therapy.

## RESULTS

A total of 88 cases >2 years of age who fulfilled the inclusion criteria attending the thalassemia day care centre were offered this regimen. 20 patients refused to participate due to fear of side effects and compliance issues, 8 cases were excluded based on their LFTs, RFTs and haematological profiles and finally 60 patients were enrolled. All of them could not complete the study and there were 6 drop outs. In 4 cases, temporary discontinuation of the drug was necessitated due to side effects.

Out of 60 cases, 37 (61.66%) were males and 23 (38.34%) were females with the male to female ratio being 1.6:1. The mean age of patients was 8.6 yrs (range: 2-18yrs). Majority of the cases (46.67%) were in the age group of 6-10 yr. The mean age of presentation with anemia was 1.68 yrs. 50% cases were HCV positive while HIV and HBV each were positive only in 1.6% cases. Haemolytic 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. 55 patients were on Deferasirox therapy (30-35 mg/kg once daily) and 4 patients were on Deferapirone (75 mg/kg/day in three divided doses), while one patient was using a combination of Deferapirone daily and Deferioxamine-thrice weekly using an infusion pump. Blood transfusion requirement was two to three times in a month before starting Hydroxyurea.

Total 31 patients showed response to HU therapy with good response in 13 patients, and partial in eighteen patients. Table 1 shows the comparative parameters for the various variables in good 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 mean serum ferritin level decreased significantly (P<0.01). Table 2 shows the comparative parameters for the various variables in partial responders. In partial responders, mean spleen size decreased but this was not statistically significantly (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 mean serum ferritin level decreased significantly (P<0.05).

12 cases could tolerate average dose of 12-15mg/kg (high dose) hydroxyurea well in contrast to 48 cases where only a lower dose (8-11mg/kg) could be tolerated due to side effects. Only 19 out of 42 cases, where HU was used in a dose of 8-11mg/kg/day, showed response to HU while all cases receiving higher dose showed good response. This indicates that high dose of hydroxyurea resulted in significantly better response but major limiting factor was adverse effects (p<0.001). Most common adverse effect was related to GIT in 10 cases (16%) followed by hepatic in 3 cases (5%) and haematological in 1 case (1.6%). GIT related side effect resolved spontaneously. Drug was discontinued temporarily in 4 cases due to myelo-toxicity and hepato-toxicity and started again at lower doses. Six cases were lost to follow up due to issue of compliance and other socio-economic problem.

## 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 which is used in the treatment of myelo-proliferative disorders. HU is also effectively used to raise HbF and Hb levels.[5-7] Although, HU increases fetal Hb levels in patients with sickle cell disease,[8] there is limited experience with HU use in thalassemia patients, particularly in a large group of major thalassemia patients. In this study, we described the effects of hydroxyurea in sixty Thalassemia major children. In our

**Table 1 – Comparison of the variables in good responder before and after therapy**

| S. No. | Par amete rs (M ean ± SD ) | Pre -H U Gr oup (N=13) | Post-H U Gr oup (N=13) | P V alu e |
|---|---|---|---|---|
| 1. | Sp le ensize (c m) | 6.38± 1.38 | 3.84± 0.89 | < 0. 001 |
| 2. | Hb (g/dl) | 6.52± 0.43 | 8.62± 0.45 | < 0. 001 |
| 3. | Hb-F ( %) | 1.36± 0.49 | 7.32± 10.07 | < 0. 05 |
| 4. | S. Fe rr itin (ng/m l) | 3940.76± 1174.23 | 2654.62±1147. 33 | < 0. 01 |
| 5. | Aver age blood re quir em ent (m l/month) | 470.62± 119.84 | 356.76± 112. 16 | < 0. 02 |

**Table 2 - Variables in partial responders before and after therapy**

| S. No. | Parameters (Mean±SD) | Pre-HU Group (N=18) | Post-HU Group (N=18) | P Value |
|---|---|---|---|---|
| 1 | Sp leen size (cm) | 5.56±1.89 | 4.81±1.51 | >0.1 |
| 2 | Hb (g/dl) | 6.89±1.08 | 7.99±1.09 | <0.01 |
| 3 | Hb-F (%) | 3.96±2.66 | 9.37±11.45 | <0.05 |
| 4 | S. Ferritin (ng/ml) | 3966.38±1740.96 | 2665.28±1650.13 | <0.05 |
| 5 | Average blood Requirement (ml/month) | 402.61±137.08 | 335.61±137.85 | <0.05 |

**Table 3 - High v/s low doses of hydroxyurea**

| S. No | Dose of Hydroxyurea | Number of cases received HU | Total Responders (Good + Partial) (n= 31) | Non responder (n =23) | P value |
|---|---|---|---|---|---|
| 1. | 8-11mg/kg (Low dose ) | 42 | 19 | 23 | <0. 001 |
| 2. | 12-15mg/kg (High dose ) | 12 | 12 | 0 | |

study, HU was well tolerated in most of the patients, except for a few instances of leucopenia, thrombocytopenia or raised liver enzymes in which temporary discontinuation of drug resulted in rapid normalization of the laboratory parameters and allowed resumption of therapy.

We categorized our patients into good, partial and non responders based on their rise in Hb levels and fall in transfusion requirements. This grading into responders was based on the previous studies done by Dixit et al and Panigrahi et al.[9,10] Our results showed decrease in extramedullary hematopoeisis after HU therapy, as evidenced by the regression in spleen size. Similar results were observed in a previous study by Bradai et al.[11]
In this study, mean monthly transfusion volume decreased which is in collaboration with the study done by Zamani et al.[6]

Our results showed a significant increase in mean total hemoglobin level and Hb-F proportion. Similar rise in Hb and Hb-F levels was reported previously also; however, most of them have evaluated thalassemia intermediate patients.[12,13] Our results showed a significant decrease in ferritin level which supports the previous studies by Alebuyeh et al,[7] and Hashemi et al.[14] The serum ferritin decrement can due to be decreased requirement of blood transfusion and to a lesser extent due to increased iron utilization by increased Hb production and also suppression of ineffective erythropoiesis. Our study showed that high dose of hydroxyurea was significantly related to a good response. However, we did not go beyond dose of 15mg/kg/day based on the observations of Hoppe et al and Karimi et al,[5,12] who suggested that higher doses do not help in further increase of Hb levels and may lead to toxicity. Zamini et al and Karimi et al,[6,12] used doses of 8-15 ml/kg/day and 8-12 ml/kg/day respectively.

Few instances of side effects were managed by temporary discontinuation of the drug. This finding has been reported in previous studies.[13,15] High seropositivity for hepatitis C in our study was possibly due to the fact that lots of our patients had received transfusion at outside facilities too and few of them contracted the infection before mandatory screening of blood for HCV was enforced. Iron overload in our patients could be assessed using only one parameter i.e. serum ferritin. Though, it is not a good indicator of iron overload yet due to non availability of liver and heart MRI to our patients, we could not quantify their tissue iron stores.

## CONCLUSIONS

We suggest using HU in thalassemia major patients to space out and decrease the need for regular transfusion, and concomitant iron overload during therapy. Our data suggests that HU therapy is safe and effective in treatment of extra medullary haematopoiesis - a complication in thalassemia major patients and merits a trial in management of these cases.

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**Funding:** None

**Conflict of Interest:** None stated