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A study to find out the Role of Hydroxyurea in Thalassemia Major Patients

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ABSTRACT

Objective: We have done this study to determine the efficacyof hydroxyurea in Thalassemia major patients.
Design: Non randomized, interventional, prospective study.
Method: 60Beta-thalassemia majorpatients aged between2-16 years (mean age 8.6 years)treated with Hydroxyurea(HU), 8-15mg/kg/day for 6months.Before starting hydroxyurea, all patients underwent routine laboratory testsand quantification of hemoglobin variants. Response was evaluated by observing the children for a rise in hemoglobin (Hb)and fetalhemoglobin (Hb-F)levels and decrease in serum ferritin,transfusion requirement and spleen size. Pre HU and post HU groupswere made for comparing the parameters after HU therapy.
Results: Itwas observed that 13/60 (21.66%) had a good response(hemoglobin increased >2 g/dl), 18/60 (21%) had partial response (hemoglobin increased by 1–2 g/dl),23/60(38.34%) had no response and 10% dropped out. The mean spleen size decreasedsignificantly (P<0.001), mean monthly transfusion volume decreased(P<0.02), mean Hb level increased (P<0.001), mean Hb-F level increased (P<0.05) and mean serum ferritin level decreased (P<0.01) in good responders. Better response was seen with higher dosage regime of the drug.
Conclusion: Hydroxyurea has a role in the composite management of thalassemia Major patients to decrease the need for regular transfusions and thus avoid concomitant iron load.

KEYWORDS 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 β-chain is precipitated within the RBCs, resulting in hemolysis and ineffective erythropoiesis. These cases need regular bloodtransfusion and iron chelation. Gamma-globin chainenhancement in RBC can potentially lead to an improvement inRBC survival and lessen anemia by reducing α/β globin chainimbalance. It has been known that Hydroxyurea ispharmacologic agent that increases γ-globin production[1,2].Also, patients who have some genetic mutations leading toHereditary Persistence of Fetal Haemoglobin (HPFH) or highlevels of HbF, have a milder phenotype of the disease[3,4]. Thestudy was based on the observation by various workers that use ofdrugs that increase the levels of HbF, indirectly help thalassemicpatients by modifying the clinical course of the disease.Hydroxyurea is a urea analogue that is safe and has been usedsuccessfully by various authors in past[5-7]. Therefore, weplanned this study to assess the efficacy and safety profile ofhydroxyurea in patients with thalassemia major.

Methods-:
Thalassemia major patients attending the thalassemia day care centre at Umaid Hospital, Jodhpur, over the period of six months 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 analyzer), liver function tests (LFT), blood urea, serum creatinine, blood sugar levels, serum calcium, serum ferritin (by Chemiluminescence, CLIA Kits), HBS Ag, HCV and HIV wereperformed 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-transfusionHb 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 reversiblehematological toxicity and no further increase in Hb [5].

End Point Variables: Clinically, the response was categorized as good if rise in hemoglobin was >2 g/dl, partial when rise was

between 1 and 2 g/dl and no response when no increment in hemoglobin 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:

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 cases (46.67%) were in age group of 6-10yrs. The mean age of presentation of our cases with anemia was 1.68yrs. 50% cases were HCV positive while HIV and HBV each were positive only in 1.6% cases. 31 patients (51.66%) showed response to HU therapy. Thirteen patients (45.9%) showed good response, and eighteen patients (30%) showed partial response. In good responder mean spleen size decreased significantly(P<0.001) ,mean monthly transfusion volume decreased significantly (P<0.02), mean Hblevel 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-1).In partial responders mean spleen size decreased but did not reach to significant level (P>0.1),mean monthly transfusion volume decreased significantly (P<0.05), mean Hblevel increased significantly (P<0.001), mean Hb-F level increased significantly (P<0.05), and mean serum ferritin level decreased significantly (P<0.05) (table-2).In 42 cases HU was used in a dose of 8-11mg/kg/day, out of them only 19 cases showed response to HU while all cases developed response to HU when HU was given in a dose of 12-15mg/kg/day.This indicate that high dose of hydroxyurea showed significantly better response but major limiting factor was adverse effects(p<0.001) (table-3).Most common adverse effect of HU was related to GIT 10(16%) followed by hepatic 3 (5%) and hematological 1(1.6%).GIT related side effect resolved spontaneously. Drug was discontinued temporarily due tomyelotoxicityand hepatic toxicity and started again at lower doses when toxicity resolved.

Discussion:

β-thalassemia is a common genetic disorder and 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 Hb-F and Hb levels[1,2,3,4]. Although HU increases fetalHb levels in patients with sickle cell disease[5],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 thrombocytopenia or raised liver enzyme for which on temporary discontinuation of the drug, resulted in rapid normalization of the lab parameters and allowed resumption of therapy.

Our results showed decrease inextramedullaryhematopoiesis after HU therapy, which could be explained by the regression in spleen size. Similar results were observed in a previous study by Mohamed et al[6]. In our study, mean monthly transfusion volume decreased. Decrease in transfusion volumehasbeen reported by Seyyed et al[7]. Our results showed a significant increase in mean total hemoglobin level and Hb-F proportion. Previous reports have reported a rise in Hb and Hb-F levels[8,9,10].However, most of them have evaluated thalassemia intermediate patients. Our results showed a significant decrease in ferritin level.This decrease has been reported by Alebuyeh et al[9] and Azamsadat et al[11].Our results showed that high dose of hydroxyureawas significantly related to response.EitanFibach et al[12] observed dose dependent effect of HU.The serum ferritin decrement is due to decrease of blood transfusionrequirement and to a lesser extent due to increased iron utilization by increased Hb production and suppression of ineffective erythropoiesis. Few instances of side effects were managed bytemporary discontinuation of the drug. This findinghas been reported in previous studies[6,8].We suggest use of 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 medullaryhematopoiesis whichis acomplication in thalassemia major patients.

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

S.No.	Parameters	Pre-HU Group(N=13)	Post-HU Group(N=13)	P Value
1.	Spleen size (cm) Mean±SD	6.38±1.38	3.84±0.89	<0.001
2.	Hb (g/dl) Mean±SD	6.52±0.43	8.62±0.45	< 0.001
3.	Hb-F Mean±SD	1.36±0.49	7.32±10.07	<0.05
4.	S.ferritin(ng/ml) Mean±SD	3940.76±1174.23	2654.62±1147.33	<0.01
5	Av. Blood Requirement (ml/month) (Mean±SD)	470.62±119.84	356.76±112.16	<0.02

Table: 2Comparative parameters for the various variables in partial responders before and after Hydroxyurea therapy

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

Table: 3-: Difference between high v/s low dose of Hydroxyurea.

S. No.	Dose ofHydroxyurea	No. of cases in which Hydroxyurea was given	Responder(n=31)(Good +Partial)	Non-Responder (n=23)	P value
1.	8-11 mg/kg (Low Dose)	42	19	23	<0.01
2.	12-15 mg/kg (High Dose)	12	12	0	

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