Original article

Role of hydroxyurea in thalassemia intermedia

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ABSTRACT

Background: Thalassemia intermedia is a term used to define a group of patients with β thalassemia in whom the clinical severity of the disease is somewhere between the mild symptoms of the β thalassemia trait and the severe manifestations of β thalassemia major.[1,2] Thalassemia intermedia encompasses a wide clinical spectrum. Mildly affected patients are completely asymptomatic until adult life, experiencing only mild anemia and maintaining hemoglobin levels between 7-10g/dL. These patients require occasional blood transfusions, during acute infections or blood loss. Patients with severe thalassemia intermedia generally presents between the ages of 2 to 6 years and although they are able to survive without regular transfusion therapy, growth and development can be retarded.[2] There is currently no definitive treatment to correct the globin chain imbalance in thalassemia, but the promising approach involves the use of therapeutic agents to definitively correct the globin chain imbalance by re-activating the fetal globin genes. Hydroxyurea, a cytotoxic drug, is reported to be useful in reducing this degree of imbalance, thus decreasing the disease severity. Due to the lesser α/β globin imbalance in β-thalassemia intermedia (TI), compared with thalassaemia major, better clinical responses are expected in patients with TI.[3,4]

Objective: To determine the clinical response and frequency of side effects of hydroxyurea in thalassemia intermedia patients in local population.

Patients and methods: Descriptive case series study was conducted in Pediatrics Department of Fatima Memorial Hospital, Lahore from August to December 2016. Total 150 patients clinically diagnosed to have thalassemia intermedia fulfilling inclusion criteria were enrolled, interviewed and examined. Baseline investigations were sent to monitor the side effects of hydroxyurea. Hydroxyurea was started at dose of 15mg/kg/day and patients were called after every fortnight for first 8 weeks and then monthly for 4 months. If no response seen on first visit, dose was increased to 20mg/kg/day and called again after 2 weeks. If still no rise in Hb observed, labelled as" no response", if Hb increase then label as according to clinical response criteria. Patients were graded according to clinical response criteria after 3 months starting of hydroxyurea. For blood transfusion frequency, patients' blood transfusion record was explored for their mean pre-transfusion Hb levels and red cell consumption after and before start of hydroxyurea in 3 months. For leucopenia, complete blood count was repeated after 1 month starting hydroxyurea. For diarrhea, clinical examination and assessment was done after 1 month of starting hydroxyurea. For neuropathy clinical assessment was done periodically on monthly visits.

Results: Out of 150 patients, 79 (53%) were transfusion dependent and 71 (47%) were transfusion independent. Total of 123 (82%) showed response and 27 (18%) showed no response even after increasing dose from 15mg/kg/day to 20mg/kg/day. Out of 123 responders, 74 (49.3%) were good responder, 49 (32.7%) were partial responder. In good responders mean increment in hemoglobin ranged between 1.5g/dl to 2.5g/dl.

Conclusion: Hydroxyurea is an effective and well tolerated drug for the treatment of thalassemia intermedia with very few side effects. With use of this medicine, regular blood transfusions and its hazards can be prevented in these patients.

Keywords:

Hydroxyurea, thalassemia intermedia, response, side effects.

INTRODUCTION

Thalassemia intermedia (TI) is a term used to define a group of patients with β-thalassemia in whom the clinical severity of the disease is somewhere between the mild symptoms of the β thalassemia trait and the severe manifestations of β thalassemia major. Thalassaemia intermedia encompasses a wide clinical spectrum from mild to severe disease.[1-4] Due to this clinical heterogeneity TI requires the need for an individualized treatment approach after evaluating the rate of hemolysis and need for blood transfusion.[3] In Pakistan, a differentiation of major and intermedia is not widely entertained by most of healthcare professionals involved in its management and TI patients also receive regular blood transfusion and become transfusion dependent with all its attendant hazards, including iron overload responsible for multiple organ dysfunctions. The hypothesis of this study was that every patient with raised HbF is not that of thalassemia major. In thalassemia major, rate of fall of Hb is ≥1gm/dl/week and HbF generally is >50% on Hb electrophoresis. Patient with raised HbF and with the rate of fall of Hb less than 1g/dl/week can be of TI. These patients maintain their Hb in a higher range, present later than one year of age and do not require to be on regular blood transfusion regimen.[1-4] Hydroxyurea, an antineoplastic agent, has been reported to induce Hb F and

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overall production of Hb. As a potent Hb inducer, the drug has been widely evaluated in thalassemia intermedia, with varying results and safety profile.[5] If TI patients are given a trial of Hydroxyurea, it raises the level of fetal hemoglobin and hence total Hb level to maintain growth and development. This can prevent regular blood transfusion, and its hazards of transmitting infections and iron overload that is responsible for 75% of death in thalassemia due to cardiac siderosis because a bag of blood contains 200 mg of iron load.[2-5] Transfusion of blood may be even more dangerous in rural area of Pakistan where basic health units are not properly equipped to diagnose and deal early and delayed complications of regular blood transfusion. Purpose of this study is to evaluate beneficial effects and safety of hydroxyurea in TI. This will help to increase awareness and build confidence in health care professionals involved in the regular management of thalassemia patients to use this medicine in TI patients and avoid regular blood transfusion and its hazards.

PATIENTS AND METHODS

After ethical approval from concerned committees, written permission was taken from parents/guardians of the patients. The study was carried out in Pediatrics Department of Fatima Memorial Hospital (FMH), Lahore from August till December 2016. A total of 150 cases of TI diagnosed on basis of clinical examination and hemoglobin electrophoresis and meeting the inclusion criteria were selected. Patients were registered for the study and demographic information (name, age, gender and address) was noted on Proforma. Baseline clinical and laboratory assessment was done for spleen/liver sizes, extramedullary enlargements, CBC, MCV, reticulocyte count, HbF, renal and liver function tests. Clinical response was defined according to criteria into three types; good response: Tranfusion independence with final hemoglobin >8.0g/dl in tranfusion dependent patient and a rise in hemoglobin ≥2g/dl in tranfusion independent patient, Partial response: transfusion independence with rise in Hb >2 g/dl but final Hb of <8g/dl or reduction in tranfusion frequency by 50% in tranfusion dependent patients and rise in Hb between 1-2 g/dl in tranfusion patients, and No response: no rise of Hb in tranfusion independent or same level of tranfusion Dependency in tranfusion dependent patients.[3] Following inclusion and exclusion criteria were employed. Patients diagnosed as TI on history, clinical examination and Hb electrophoresis at FMH but had been on regular blood transfusions by any other healthcare facility since the time of diagnosis and now were put on hydroxyurea. Patient diagnosed TI on history clinical examination and Hb electrophoresis at FMH and received no transfusion prior to this study. Patients with spleen size more than 6cm at beginning of study, splenectomized patients, patients with established cardiomyopathy and patients with established endocrinopathies were excluded. Hydroxyurea (HU) was started orally at dose of 15mg/kg/day and increased by 5mg/kg/day till maximum of 20mg/kg/day as tolerated. Patients were called fortnightly for first 8 weeks and then monthly for 4 months. During the period of treatment, clinical and laboratory monitoring was done in form of history and examination, CBC, reticulocytes count, Hb F estimation, renal and liver functions and number of any transfusions upon each visit. Dose of HU was adjusted according to response and side effects. Side effects were monitored by clinical and laboratory assessments. Blood levels of HU were not performed. In patients with significant side effects and no response treatment is stopped and it is continued in rest of patients. Effectiveness was assessed after 4 months by monitoring blood transfusion frequency and mean hemoglobin increment before and after starting HU. Patient were graded according to clinical response criteria after 4months of starting the HU. Regarding mean hemoglobin increment good response is >1g/dl increase in mean hemoglobin and less than this were non-responders. Regular blood transfusion requirement was defined as 15-20ml/kg of packed red cells transfused at 4 weekly intervals.[2] For blood transfusion frequency, over all response rate was defined as >50% reduction in patient blood transfusion needs post HU therapy. For Leucopenia, complete blood count was advised after 1 month of starting HU. For diarrhea, clinical assessment was done after 1 month of starting HU and also informed to parent if child developed change in bowel routine report to hospital immediately. For neuropathy clinical examination and assessment was done periodically first after 1 month and monthly for 4 months then after. All these assessments and investigations were entered according to given schedule in data collection proforma. All the collected information was entered in the SPSS version 23. Mean±SD of quantitative data like age was calculated. The percentages and frequency were calculated for qualitative data like gender, good response, no response for hemoglobin increment and response rate for transfusion frequency as well as side effects in term of leucopenia, diarrhea and neuropathy. Data were stratified for newly diagnosed and blood transfused TI patients to address the effect of modifiers. Chi-square test was applied for the comparisons between categorical variables. Results were presented as mean, standard deviation and percentages.

RESULTS

There were 150 patients diagnosed as TI clinically and on Hb electrophoresis. Patients aged from 10 months to 26 years were enrolled, mean age were 4.9 ± 4.6 years. Eighty-five (57%) were male 65 (43%) were female, with male to female ratio of 1.3:1. After thorough history and examination and planned investigations, all patients were given HU. Out of 150 patients, 79 (53%) were transfusion dependent and 71 (47%) were transfusion independent. Total of 123 (82%) showed response. Out of 123

responders 74 (49.3%) were good responders, 49 (32.7%) were partial responders, whereas 27 (18%) patients showed no response even after increasing dose from 15mg/kg/day to 20mg/kg/day (Figure 1). Out of 74 good responders, there were 43 (58.1%) males and 31 (49.1%) females. In 49 partial responders, 32 (65%) were males and 17 (34.7%) females, whereas among 27 non-responders, 11 were male (40.7%) and 16 (59.6%) were female. Table 1 summarizes the gender wise response to HU. On cross tabulation of response to HU with age of patients, it is found that those who presented less than 5 years of age, 100 (67%) patients, 76 (50.6%) showed good response and 24 (49.4%) showed no response. These

Table 1. Gender distribution according to the response

Gender	Response of the patient to hydroxyurea			Total
	Good	Partial	No response	
Female	31	17	16	64
Male	43	32	11	86

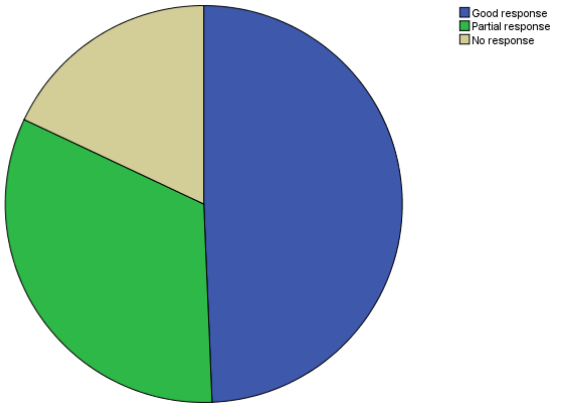

Figure 1. Response to hydroxyurea (N=150)

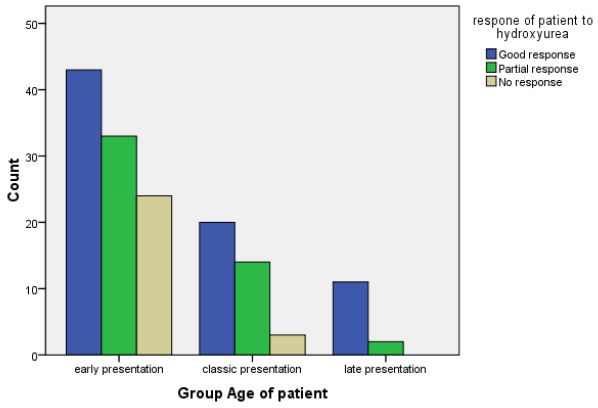

Figure 2. Response of hydroxyurea according to the age group of patients (N=123)

were categorized as patients with early presentation. Those who presented between 5 to 10 years of age, total of 37 (25%) patients, 34 (13%) showed good response and 2 (3%) showed no response and were categorized as those with classical presentation. Patient presented after 10 years of age, 13 (8.7%), showed good response in 11(7.3%) and partial response in 2 (1.3%) level. These were labelled as those with late presentation. Figure 2 depicts these age group wise response with p-value<0.005, as almost all patient groups responded to HU to some extent. The main adverse effect observed is diarrhea which is seen in 8 (5.3%) patients. No other significant side effect was noted.

DISCUSSION

Traditionally thalassemia intermedia patients are treated with regular packed red blood cell (PRBC) transfusion and iron overload is managed with chelation, same as in Thalassemia Major.[2] This treatment has not only its inherent complications and side effects but also has substantial financial burden both for patients and health care organizations. HbF inducing agents, like HU, never gained popularity due to perceived and involved side effects and toxicity. First time in 1994 few centers started using HU with success.[4] This study showed overall 82% response in TI patients, which is well within those reported in the literature.[5-11] Most of the patients shown response to HU within one month of therapy. Patient who did not show response with initial dose of 15mg/kg/day, did not show response even after increasing the dose up till 20mg per kg per day. Most of the patient sustained their response even after 6 months. Partial responder has little bit delay onset of response. Only 5.3% developed diarrhea as the only adverse effect in this study. A study conducted in 44 patients at Sir Ganga Ram Hospital, Lahore only 3.6% showed gastrointestinal-related side effects.[3] In another study of 80 patients, main side effects (2.5%) reported were again related to GIT and thrombocytopenia.[6] A study from Iran in 133 patients reported adverse reactions in 33% of the patient on HU in a mean dose of 10.74 mg/kg/day for 6 to 54 months duration. Most common unwanted effect reported was headache (12%) followed by skin pigmentation (7.5%), hair loss (6%), maculo-papular rash (6%), dizziness (5.25%), anorexia (4.5%), facial erythema (3.25%), nausea and vomiting (1.3%).These side effects were well tolerated by the patients and were categorized as mild and transient and none was reported to lead to discontinuation of therapy.[8] No such effects were observed in present study. This may be explained by variation in geographical and racial presentation and needs further large-scale studies. In the present study response to HU is found as inversely related to age. Good response was observed more in younger patient population. This observation is in conformation with the study of Dixit and associates that showed older age as a predictor for poor response.[9] In contrast, in an Indian study of 55 patients with only 15 patients under the age of 3 years reported by Marwah and coauthors and the study done in Sir Ganga Ram Hospital, Lahore reports better outcome in children who were diagnosed in first three years of age.[3,9] However, since the number of patients in this group is too small,

larger studies are needed to validate the relation of age with response to HU. However, one plausible explanation of good response in younger patient could be exposure to less number of blood transfusion prior to HU treatment, as regular blood transfusion suppresses erythropoiesis, especially in HU responsive erythroid precursors.[10,11] No correlation of response to HU was found with gender, weight of the patient and fetal hemoglobin levels. These finding correspond well with other international and national studies which have been done on efficiency of HU.[3,5,9-14]

In present study DNA analysis for TI is not done. However, an accurate diagnosis based on history, clinical examination and confirmed by DNA diagnosis can save a lot of patients from regular blood transfusions, iron overload and its complications by using HU therapy. It will also spare the patients and hospitals a lot of undue expense. Treating TI with HU will also reduce the burden on blood transfusion services and reduce the incidence of Hepatitis B and C infection in these patients. Special efforts should be done to determine genetic markers for TI like Xmn1 polymorphism and coinheritance of alpha thalassemia, to identify patients who may get benefit by HbF augmentation with HU therapy. The basis of this study was that every patient with raised HbF is not that of thalassemia major. Early referral to specialist center and early management with initiation of HU in TI patients can reduce transfusion frequency and its early and late complications in this group of patients. The drug has shown promising results with well-tolerated minimal side effects in this thalassemia intermedia.

CONCLUSION

Hydroxyurea is an effective and well tolerated drug for the treatment of thalassemia intermedia with very few side effects. With use of this medicine, regular blood transfusions and its hazards can be prevented in these patients.

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