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THE CLINICAL PARAMETERS OF HYDROXYUREA IN THALASSEMIA PATIENTS AND TO CALCULATE THE OCCURRENCE OF ITS SIDE EFFECTS

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Abstract:

Objective: *The aim of our study was to find out the clinical parameters of hydroxyurea in thalassemia patients and to calculate the occurrence of its side effects.*

Study Design: *A descriptive study.*

Place and duration: *This study was conducted at the department of Pediatrics, District Headquarters hospital Sargodha for the duration of five months starting from April,2020 to September, 2020.*

Methodology: *In our study we observed 150 patients who were meeting the criteria for inclusion of thalassemia intermedia. To monitor the side effects of hydroxyurea we sent baseline investigators. Patients took their hydroxyurea dose as 15mg/kg per day and after fifteen days patients were visited for first eight weeks and then they were called monthly for four months. After this if we do not observe any response of described dosage in first visit, we increase the dose of hydroxyurea to 20mg/kg per day and then called again for visit after two weeks. If the level of Hb increase then it is labeled according to clinical criteria, and if the level of Hb doesn't increase then Hb labeled as no response. When the hydroxyurea was start in third month, we grade the patients according to clinical criteria. All the gathered data was entered in the SPSS version 20 for analysis.*

Results: *In our present study we observed 150 patients in which 71 patients (47%) out of 150 were having independent transfusion and 79 patients (53%) out of 150 were having dependent transfusion. 27 patients (18%) were those who don't show any response of Hb even after increasing of dose of hydroxyurea from15mg/kg per day to 20mg/kg per day and 123 patients (82%) were those who show response of Hb in normal per day dosage. Out of 123 patients who showed positive response, 49 patients (32.7%) were partial responder and 74 patients (49.3%) were good responder. 1.5g/dl to 2.5g/dl is a mean increment in hemoglobin in good responders.*

Conclusion: *At the end of our study, we conclude that with few side effects hydroxyurea is a good medicine for the treatment of thalassemia. Regular blood transfusions can be prevented in thalassemia patients with regular use of hydroxyurea.*

Keywords: *Thalassemia Intermedia, Response, Hydroxyurea, Side Effects*

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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. Thalassemia intermedia encompasses a wide clinical spectrum from mild to severe disease [1,2]. 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] 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 [4,5]. Hydroxyurea, an antineoplastic agent, has been reported to induce Hb F and overall production of Hb. As a potent Hb inducer, the drug has been widely evaluated in thalassemia intermedia, with varying results and safety profile [6]. 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 [7,8]. 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.

METHODOLOGY:

This descriptive study was conducted at the department of Pediatrics, District Headquarters hospital Sargodha for the duration of five months starting from April,2020 to September, 2020. 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: Transfusion independence with final hemoglobin >8.0g/dl in transfusion dependent patient and a rise in hemoglobin ≥2g/dl in transfusion independent patient, Partial response: transfusion independence with rise in Hb >2 g/dl but final Hb of <8g/dl or reduction in transfusion frequency by 50% in transfusion dependent patients and rise in Hb between 1-2 g/dl in transfusion patients, and No response: no rise of Hb in transfusion independent or same level of transfusion Dependency in transfusion dependent patients.

In patients with significant side effects and no response treatment is stopped and it is continued in rest of patients. 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. 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 20. 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

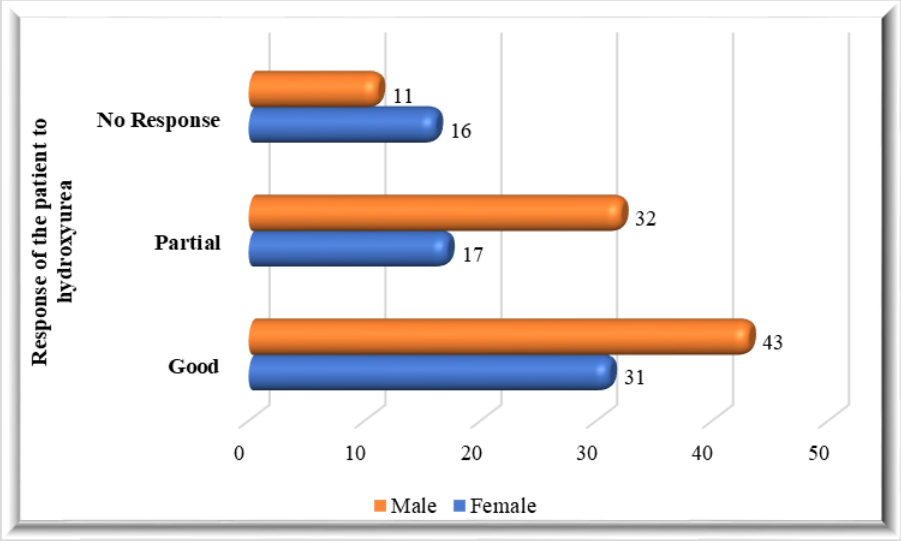
for transfusion frequency as well as side effects in term of leucopenia, diarrhea and neuropathy. Data were stratified for newly diagnosed and blood transfused TI patients to address the effect of modifiers. Chi-square test was applied for the comparisons between categorical variables. Results were presented 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. 86 (57%) were male 64 (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. 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.

Table No 01: Response of the Patient to Hydroxyurea According to Gender

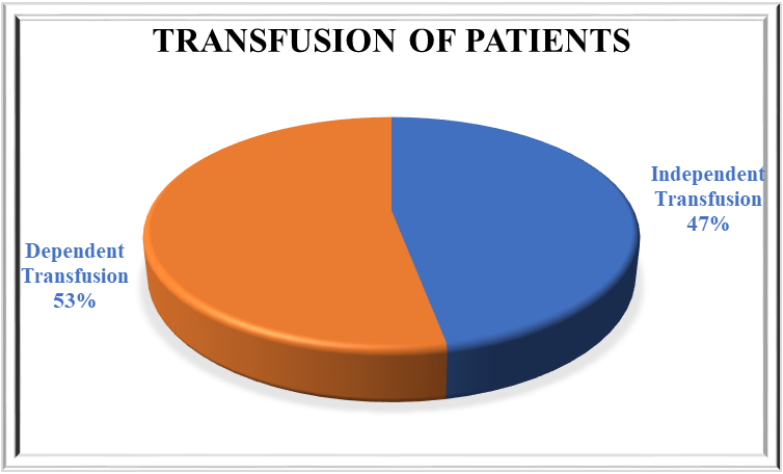
Gender	Response of the patient to hydroxyurea			Total
	Good	Partial	No Response	
Female	31	17	16	64
Male	43	32	11	86



In our present study we observed 150 patients in which 71 patients (47%) out of 150 were having independent transfusion and 79 patients (53%) out of 150 were having dependent transfusion.

Table No 02: Transfusion of Patients

Transfusion	Qty	%age
Independent Transfusion	71	47%
Dependent Transfusion	79	53%
Total	150	100%



DISCUSSION:

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 [9,10]. 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 [11]. 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 βthalassemia intermedia (TI), compared with thalassemia major, better clinical responses are expected in patients with TI [12,13]. 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 [13].

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. 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 Benazir Bhutto hospital Rawalpindi 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 popular 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].

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:

At the end of our study, we conclude that the good medicine for the treatment of thalassemia is hydroxyurea. Regular blood transfusions can be prevented in thalassemia patients with regular use of hydroxyurea.

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