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Original Research Article

Effect on Blood Parameters after Chelation Therapy in Thalassemia major patients

Sourabh Agrawal[1], Anil Prasad[2]

[1]Associate Professor, Department of Paediatrics, Amaltas Institute of Medical Sciences, Dewas

[2]Assistant Professor, Department of Paediatrics, Amaltas Institute of Medical Sciences, Dewas

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Corresponding author: Dr Anil Prasad

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Abstract

Background: It is estimated that 3% of the world population and 3-17% of the Indian population are beta (β)-thalassemia gene carriers. B-thalassemia is a disease resulting from a decrease in β-globin chain production and a subsequent imbalance in α/β-globin chain ratio. Excess α chain gets precipitated within RBC, resulting in hemolysis and ineffective erythropoiesis, require RBC transfusions in every two to three weeks, which means 52 units of blood in a year. These lifelong blood transfusions can lead to iron overload, which ultimately damages tissues in the liver, heart, endocrine organs, and joints.

Aim: This study aims to study effect on blood parameters after chelation therapy in thalassemic major patients.

Methodology: In our study 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. 23/60(38.34%) thalassemia major cases were non-responder. There was no change in mean Hb, mean Hb-F, mean serum ferritin level and mean blood transfusion requirement in these cases after HU therapy. In 12 cases HU was used in 12-15mg/kg of dose, these all patients developed response to HU. Out of 42 patients where a dose of 8-11mg/kg was used only 19 patients showed response to HU (12-15mg kg).

Conclusion: This study shows that HU can be a used in TM to decrease the need of blood transfusion, Because of oral use, inexpensive cost, minimal side effect and positive clinical and hematological response, we strongly recommend the use of HU with blood transfusion in patients of TM.

Keywords: Beta (B)-Thalassemia, Blood Parameters, Thalassemic Major Patients After, Chelation Therapy.

Introduction

Beta thalassemia gene carriers are estimated to make up 3% of the global population and 3- 17% of India's population [1-10] Mutations in the beta globin gene cause beta thalassemia. Thalassemia major causes anemia at a young age and requires regular blood transfusions. However, those who are

heterozygous (who have thalassemia minor) often exhibit no symptoms and have hemoglobin levels that are either normal or just mildly deficient. Thalassemia intermedia is a condition that falls between thalassemia major and thalassemia minor; B-thalassemia is a disease resulting from a decrease in β-globin chain production and a subsequent imbalance in α/β-globin chain ratio. Excess α chain gets precipitated within RBC, resulting in hemolysis and ineffective erythropoiesis, require RBC transfusions in every two to three weeks, which means 52 units of blood in a year. These lifelong blood transfusions can lead to iron overload, which ultimately damages tissues in the liver, heart, endocrine organs, and joints. Regarding the complications of blood transfusion and limitation of blood supply, the treatment requirements of these patients are justified with such agents which decrease blood transfusion requirement. B-Thalassemia is milder in individuals who retain the capacity to synthesize Hb- F after birth thereby increasing their γ-globin chain synthesis and reduces α/β-globin chain imbalance and neutralize the excess α-chain, partially correct ineffective erythropoiesis and improves anemia. Hydroxyurea (HU) is a pharmacological agent that increases γ-globin production. [3,11-20] This study aims to study effect on blood parameters in thalassemic major patients after chelation therapy

Methodology

The present study was Non-randomized interventional prospective Study conducted in the Department of Pediatrics, choithram hospital and research centre Indore, for a period of six months, from July 2013 to December 2013. Sixty thalassemia major patients attending the Department of Pediatrics, choithram hospital and research centre Indore,were enrolled for a period of six months, from July, 2013 to December 2013.. The data was analyzed with the help of Microsoft Exel 20007, The program STAR PACK, version 3.0, can perform statistical analyses such as the student t test and other appropriate tests. Sample continuous data were summarized using meanSD, while sample categorical data were given as a percentage. If the p-value was less than 0.05, then the difference between the two numbers was statistically significant.

Diagnosis of thalassemia major 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 .We were including cases of β-Thalassemia major .

Patients were belong to age group 2-18. Written informed consent was obtained before the enrollment. Cases who already had kidney or liver illness were not included in our study. Hepatic disease is suspected when either alanine aminotransferase (ALT) or aspartate aminotransferase (AST) values rise by more than twofold from their baseline. The normal values for AST (SGOT) is from 15 to 45 units per liter of serum and normal values for ALT (SGPT) is from 5 to 45 units per liter of serum. Renal disease is defined when serum creatinine value is >50% of its normal value, which shall be taken as 0.5-1mg/dl. A daily dosage of 8-15 mg/kg HU was given. Without adverse effects, the HU dosage was raised from 8 mg/kg/day to 15 mg/kg/day. There was a 6-month period of observation. If the patient's hemoglobin level rose by more than 2 g/dL, the clinical response was deemed satisfactory. partial when Hb increased 1–2 g/dl and no response when no increment in Hb after HU therapy. Lab monitoring was done.

Results

The present study was conducted in the Department of Pediatrics, choithram hospital

and research centre Indore. Sixty known thalassemic children of age b/w 2-18 were enrolled, from July, 2013 to December 2013. In this study maximum number of cases belonged to age group of 6-10yr (46.67%) followed by 11-18 yr of age (28.33%). Male to female ratio was 1.6:1. Out of 60 patients, 53 (88.33) were from Hindu community and 7 (11.67%) were from Muslim community. 32 (53.33%) cases were from rural region and 28(40.17%) were from urban region.

Blood transfusion was started in 85% cases below 2yrs of age, 8.3% cases in 2 - 5 yrs of age and 6.7% cases above 5 yrs of age. Our research found that the average age of anemia diagnosis was 1.68 years. Hemolytic facies were present in 80% of cases in this study. In this study 50% cases were HCV positive while HIV and HBV each were positive in 1.6% cases. In 80% of cases dose of HU used varies from 8-11mg/kg and in 20% cases a dose of 12-15 mg/kg was given. In this study most common adverse effect was related to GIT (16%) followed by hepatic (5%) and hematological (1.6%).

GIT related side effect resolved spontaneously. Drug was discontinued temporarily due to myelotoxicity and hepatic toxicity and started again at lower doses. Mean spleen size was (cm) decreased significantly after HU therapy (P<0.01). The mean Hb level increased after HU therapy which was statistically highly significant (p<0.001). We observed significant drop in mean blood requirement (ml/month) after HU therapy. (P<0.05). There was a rise in mean Hb-F level during therapy period which was statistically significant (P<0.01) Hb-A and Hb-A_2 did not change significantly after HU therapy, (P>0.1), (P>0.9) respectively. We observed significant decrease in mean serum ferritin level after HU therapy. (P<0.1).

In our study 13/60 (21.66%) cases showed good response. In these cases mean spleen size decreased significantly (P<0.001). "Spleen size was 5.66±1.66 cm in group A as compared to 4.62±1.49 cm in group B which was significant (p<0.01). Liver size was 3.74±1.18 in group A as compared to 3.33±0.95 cm in group B which was not significant (p>0.1) as seen in Table 1, We observed a statistically significant decrease in monthly mean blood transfusion (P=0.02), an increase in mean Hb level (P=0.001), an increase in Hb-F level (P=0.05), and a decrease in mean serum ferritin level (P=0.01)."

Our study revealed a 30% patients showed partial response. It was found that the average spleen size decreased but did not reach a significant level (P>0.1), the average monthly blood transfusion decreased completely (P0.05), the average Hb level increased significantly (P0.001), the average Hb-F level increased significantly (P0.05), and the average serum ferritin level decreased significantly (P0.05) in these cases.

In our study 23/60(38.34%) cases were non-responder. There was no change in mean Hb, mean Hb-F, mean serum ferritin level and mean blood transfusion requirement in these cases after HU therapy. In 12 cases HU was used in 12-15 mg/kg of dose, these all patients developed response to HU. Out of 42 patients where a dose of 8-11mg/kg was used only 19 patients showed response to HU (12-15mg kg) as seen in Table 2. There was no significant difference among responder and non-responder in term of age at which diagnosis of thalassemia was made. There was highly significant difference in response to dose of HU (p<0.001).

Table 1: Comparison of spleen and liver size

S. No.	Parameters	Group(n=54)		P value
		Pre HU	Post HU	
1.	Spleen size(cm) Mean±SD	5.66±1.66	4.62±1.49	<0.01
2.	Liver size(cm) Mean±SD	3.74±1.18	3.33±0.95	>0.1

Table 2: Relation of responders to dose of HU

S. No	Dose of HU	n	Group A (n=23)	Group B (n=31)	P value
			Non responder	Responder (Good +Partial)	>0.001
1.	8-11mg/kg	42	23	19	
2.	12-15mg/kg	12	0	12	

Discussion

"In our study 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. In 80% of cases the dose used varied from 8-11mg/kg and in 20% cases a dose of 12-15 mg/kg was given. Variable doses of HU had been used like 3-10mg/kg/day, 8-15 mg/kg/day and 20mg/kg/day by Carlyon et al[3], Seyyed et al[8] and Mohammad Eha. et al[2] respectively. In this study 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. Similar finding was observed by Dixit et al[10] and Seyyed et al[8]. The mean Hb level was increased after HU therapy which was highly significant (p<0.001) in our study.Similar observation was documented by Ved P Choudhary et al[6] ,Mohammad Eha. et al[2] and Seyyed et al[8].Rise of Hb was significant in our study and in study by Mohammad Eha . et al[2] (p<0.001), in contrast to study of Ved P Choudhary et al[6] and Seyyed et al[8] where rise of Hb was not significant .There was no significant difference in TLC and platelet count after HU therapy, (P>0.9) and (P>0.6),respectively, in our study. We observed statistically significant decrease in blood requirement (ml/month) (P<0.05). Similar finding was observed by Seyyed et al[8].They observed that transfusion stopped in 12/49(25%) patients spaced out in 32/49(65%) and continued in 5/49(10%) patients .In our study blood transfusion decreased but did not stop. It was due the fact to that most of the cases in our study had splenomegaly, and came 2-3 times in a month for blood transfusion. Ariel et al observed that 82%(9/11) TM became transfusion free most of these responders were either homozygous or heterozygous for the Xmnl polymorphism .Similarly Alebouyeh et al[4] observed that Xmn1 and IVSII-1 (homo- and/or heterozygosis) are relevant markers in most cases who became transfusion free after HU therapy. Such type of molecular and genetic evaluation is needed in our study to better correlate the effect of HU. Our results showed a significant decrease in ferritin level in TM patients, (P<0.01) which was associated with deceased in blood transfusion requirement. Similar results were shown by Seyyed et al[8] (P<0.001) with significant decrease in desferrioxamine injection (P<0.001) .Similar decrease in ferritin level has been reported by Azamsadat et al[7] and Khushnooma et al[5] .There was no statistically significant difference in S.bilirubine, SGPT, SGOT, blood urea and serum creatinin during therapy,(P>0.2), (P>0.9) (P>0.9), (

P>0.1)and (P>0.6) respectively.sAs in our study 21.66% cases showed good response .In these cases 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 study of Dixit et al[10],45.9% cases were good responder with significantly increase in mean Hb(P<0.001), significantly increase in mean Hb-F(P<0.01) and significantly decrease in transfusion requirement and few cases became transfusion free. Intermediate cases were enrolled in Dixit et al[10] study as compared to our study where all TM were enrolled, probably this explains why in our study no cases became transfusion free . Yavarian m et al[17] observed that 61% cases became transfusion free ,they all had Xmn1 polymorphism which might be a favourable molecule for HU response . Panigrahi et al[16] observed that genetic factor like α -3.7 deletion was related to significant rise in Hb-F and total Hb, and significant decreased in serum ferritin level. The Fr8/9 mutation was found a predictor of good hematological response in study of Mohammad Eha et al[12] . History of splenectomy also influences the effect of HU as seen in study of Seyyed et al[18] .In their study 25% cases became transfusion free because all cases were splenectomised as compared to our study where most of cases had splenomegaly, but Yavarian m et al[17] observed that there was no significant difference in reponse to HU between splenectomised and nonsplenectomised cases .Sachdeva et al[12] observed that 36% cases became transfusion free but such response did not observe in our study. Because they used HU in a dose of 15-20mg/kg and their study group had mean age of 11.6yrs and mean age of presentation with anemia was 4.35yrs while in our study HU was given in a dose of 8- 15mg/kg/day, and mean age and mean age of presentation with anemia in current study was 8.6yrs and 1.68yrs respectively. So this indicates dose of HU, mean age of cases and mean age of presentation with anemia affect the response of HU. So there were combination of variable factors in term of age , age of presentation ,dose of HU,history of splenectomy and genetic structure of globin gene affecting the final response .Improvement in social activity ,cardiac ejection fraction ,decreased extramedullary hematopoeisis after HU treatment were seen by Azamsadat et al[7]. These results are consistent with our study in which we also observed decrease in mean spleen size. (p>0.5) .We did not evaluate cardiac ejection fraction and improvement in social activity. De Paula et al[18] observed that 1/4 (25%) TM became transfusion free after 6 months of HU therapy. Thus they concluded that large study concerning the response to HU in TM patients should be carried out to clear this issue, like our study. In our study 30% cases showed partial response. In these cases mean spleen size decreased but did 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 mean serum ferritin level decreased significantly (P<0.05). In study of Dixit et al[10],24.3% cases were partial responder .The increase in mean Hb was significant (P<0.001) similar to our study, but increase in mean Hb-F was insignificant (P<0.01),unlike our study and decrease in transfusion requirement was similar to our study. Azamsadat et al[7] observed that 21.3% TM were partial responder Who showed significantly decreased transfusion requirement (P<0.001), significantly increased in mean Hb (P<0.05) and significantly decrease in mean serum ferritin level (P<0.05).These

results were similar to our partial responder group but they did not observe effect of HU on Hb-F which is a very important parameter,as observed in current study. Khushnooma et al[5] observed that 32 % TM showed partial response after HU treatment which correlated with a higher mean increase in HbF. A significant decrease in serum ferritin was also observed by them. These results were consistent with our study. In our study 23/60(38.34%) cases were non responder. There were no change in mean Hb, mean Hb-F, mean blood transfusion requirement and mean serum ferritin level in these cases after HU therapy. In our study we used small doses of HU in most of cases In 12 cases HU was used in 12-15mg/kg/day of dose,all these patients developed response to HU. In 42 cases HU was used in a dose of 8-11mg/kg/day,out of these cases used only 19 patients showed response to HU patients .There was highly significant difference in response to dose of HU ($p<0.001$). Fouzia Ishaq et al[19] used 15mg/kg of HU and noted response in 44/55(80%) of Cases.

Conclusion

Herein, we reported the outcomes of HU therapy for 60 patients with transfusion-dependent major beta thalassemic disease. The most important findings from this research included the changes in total Hb, Hb-F, transfusion needs, ferritin levels, and spleen size. We found that in those who responded, both total Hb and Hb-F levels increased, while serum ferritin levels dropped and spleen sizes shrink. Since iron excess is the greatest threat to the responder group, the dramatic fall in serum ferritin is of critical therapeutic importance. Serum ferritin dropped because of fewer transfusions and, to a lesser extent, because of higher iron consumption because of more hemoglobin formation and less inefficient erythropoiesis. HU has good effect on total Hb, Hb-F blood transfusion requirement and serum ferritin levels, and decreasing complication like organomegaly. HU treatment was well-tolerated. Only one case developed myelotoxicity in term of neutropenia and thrombocytopenia while three developed hepatic toxicity in term of raised SGPT, which resolved after a short period of HU cessation. This study shows that HU can be a used in TM to decrease the need of blood transfusion. Because of oral use, inexpensive cost, minimal side effect and positive clinical and hematological response, we strongly recommend the use of HU with blood transfusion in patients of TM.

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