Journal of Rawalpindi Medical College (JRMC); 2019;23(1): 30-33

Original Article

Effect of Combined Hydroxyurea and Chelation Therapy in Reducing Serum Ferritin Level, Liver and Spleen Size in Transfusion Dependent Thalassaemia Major Patients.

Tatheer Zahra[1], Wajeeha Amber[2], Itrat Fatima[3]

1 Bone marrow transplant unit Children hospital PIMS Islamabad;2. Department of Paediatrics, Akbar Niazi Hospital, Islamabad Medical and Dental College, Islamabad.;3. Department of Paediatrics, Children Hospital, Pakistan Institute of Medical Sciences, SZABMU, Islamabad

Abstract

Background: To compare hydroxyurea plus iron chelation therapy with iron chelation therapy alone in controlling iron overload in children with beta thalassaemia major.

Methods: In this comparative study forty thalassaemia major, cases undergoing routine blood transfusion, were observed in iron chelation plus hydroxyurea group (n=20) and iron chelation therapy alone (n=20). The study outcome was measured in terms of impact of continuous blood transfusions on the size of liver ,spleen and Serum. Ferritin levels when compared among those given iron chelation therapy with hydroxyurea and those given iron chelation alone.

Results: Mean age of patients was comparable among the two groups. Overall, males were slightly greater in proportion than females (52.5% versus 47.5%). The mean liver size, spleen size and ferritin levels were significantly low in hydroxyurea group compared to no hydroxyurea group (p-value, <0.001).

Conclusion: Hydroxyurea plus iron chelation therapy is better than iron chelation therapy alone in controlling iron overload in terms of enlargement of liver, and also limiting iron stores.

Keywords: Beta thalassaemia, Transfusion dependent , Iron chelation, Hydroxyurea

Introduction

Beta thalassaemia is a prevalent genetic disorder and commonly presents in paediatric age group.[1] The routine symptoms of beta thalassaemia is inability to synthesize haemoglobin due to failure in haematopoietic process. The incidence of the disease varies from 3-100/100000 population. Some estimates suggest that more than 25000 people with beta thalassaemia are living in Iran.[2] Every year more than 60000 babies are born with thalassaemia major worldwide and more than 80 million cases have positive thalassaemia carrier state.[3] Beta thalassaemiais is specified by chronic and severe haemolytic anaemia manifestation, lack of proper growth, enlargement of the spleen, and liver,iron overload and bone deformities, with especially visible changes in facial bones.[4]

Treatment for β-thalassemia involves regular blood transfusion and disposal of excess iron from the body, especially liver. Though survival of patients has improved many folds, regular transfusion has many medical risks which may have role in depletion of quality of life.[5] The consequences of liver and spleen enlargement vary, the improper blood production and containment results in weakness of bones, muscles and body systems. This anaemic condition puts a patient on the risk of cardiac decompensation, renal or hepatic failure. Excess iron is extremely toxic to all cells of the body and can cause serious and irreversible organic damage, such as cirrhosis, diabetes, heart disease, and hypogonadism. Fibrosis of the liver correlates directly with the age, number of units transfused, and the liver iron concentration. [6]

The amount of fetal hemoglobin in red cell plays a major role in determining the severity of thalassemia. The increase in gamma globin chain synthesis decreases the alpha chain imbalance and improves the anemia. Multiple drugs have been studied to increase hemoglobin F. Histone deacetylase (HDAC) inhibitors such as butyrate and short-chain fatty acids revealed a modest response . 5-azacytidine initially shows favourable results , but was abandoned because of toxicity. Erythropoietin has increased fetal hemoglobin and total hemoglobin, particularly in patients with relatively low levels of erythropoietin. However, the long-term benefit is unknown, and the risk of marrow expansion is a cause for concern. The most successful fetal hemoglobin agent to date is oral

hydroxyurea. Hydroxyurea is a cytotoxic drug that is short-acting and relatively easy to monitor. It is FDA-approved for the treatment of severe sickle cell disease. It is less effective and predictable in thalassemia and more likely to be beneficial in thalassemia intermedia cases and with those with xmn plymorphisim . [7]

Patients and Methods

This comparative study was conducted in the Bone Marrow Transplant Unit at the Children Hospital, PIMS, Islamabad. Patients were divided into two groups on the basis of iron chelation therapy with hydroxyurea (n=20) or without hydroxyurea (n=20). In the interventional arm patients were given hydroxyurea along with iron chelation therapy after blood transfusion whereas in the control arm iron chelation therapy alone was given after blood transfusion,the cannula was saved and used for the iv chelation for the next 7 day with the dose of 50mg/kg iv desferal which was switched to oral deferrasirox 40mg/kg for next 03 weeks. Hydroxyurea was continued with the dose of 20mg/kg daily without any gap. Patients of paediatric age (up to 12 years) were enrolled. For maintenance of quality and continuity of data, all the study process was conducted by the researcher herself. The study outcome was measured in terms of impact of continuous blood transfusions on the size of liver ,spleen and Serum Ferritin levels when compared among those given iron chelation therapy with hydroxyurea and those given iron chelation alone. Data was entered and analyzed in SPSS version 16.0. The quantitative variables like age and liver and spleen size were measured as mean and standard deviation whereas the categorical variables like gender was measured as frequency and percentages. The mean liver size was compared between the two groups using student's t-test using a significance level of 0.05 as cutoff.

Results

The mean age of patients was equal in the two groups, 4.22 ± 0.59 years in hydroxyurea group compared to 4.32 ± 0.59 years in no hydroxyurea group (Table 1). There were 9 (45.0%) females in hydroxyurea group compared to 11 (55.0%) males. However, in no hydroxyurea group both males 10 (50.0%) and females 10 (50.0%) were equally distributed. The mean size of spleen (cm) and liver (cm) ,serum ferritin levels (ng/ml) was found equal among the two study groups at baseline. The size of liver got significantly decreased after combination of hydroxyurea intervention (4.64 ± 0.49 cm to 2.38 ± 0.25 cm). It was also found significantly different post intervention among hydroxyurea and no hydroxyurea groups (p-value, <0.001). Similarly, the size of spleen was also found significantly reduced after intervention (3.45 ± 0.31 cm to 1.91 ± 0.17 cm) .The mean size of spleen after intervention was found significantly decreased in hydroxyurea group compared to no hydroxyurea group (1.91 ± 0.17 vs 2.94 ± 0.27, p-value, <0.001).

Table 1: Age of patients in the two study groups

	Hydroxyurea (n=20)	No Hydroxyurea (n=20)	p-value
Age categories (years)			
3-3.99	7 (35.0%)	8 (40.0%)	0.80
4.0-4.99	10 (50.0%)	8 (40.0%)	
5.0 or above	3 (15.0%)	4 (20.0%)	
Mean ± SD	4.22 ± 0.59	4.32 ± 0.59	0.61

Table 2: Comparison of outcomes between the two study groups

	Hydroxyurea (n=20)	No Hydroxyurea (n=20)	p-value
Baseline liver size (cm)			
Mean ± SD	4.64 ± 0.49	4.80± 0.46	0.31
Post intervention liver size (cm)			
Mean ± SD	2.38 ± 0.25	3.87 ± 0.45	< 0.001
Baseline spleen size (cm)			
Mean ± SD	3.45 ± 0.31	3.55 ± 0.29	0.32
Post intervention spleen size (cm)			
Mean ± SD	1.91 ± 0.17	2.94 ± 0.27	< 0.001
Baseline ferritin level (ng/ml)			
Mean ± SD	5560.0 ± 368.1	5495.4± 507.7	0.11
Post intervention ferritin level (ng/ml)			
Mean ± SD	3202.5 ± 225.8	4158.4± 507.7	<0.001

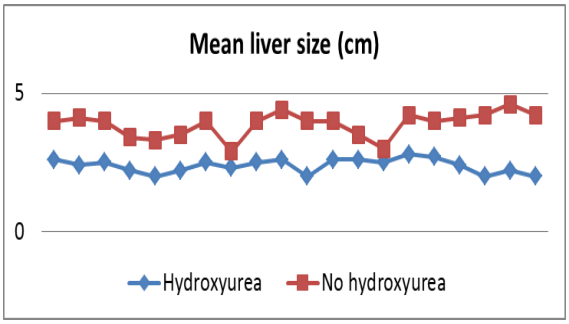

Figure 1: Post intervention comparison of liver size among two groups

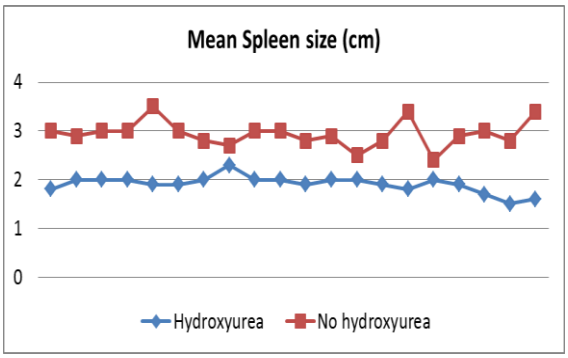

Figure 2: Post intervention comparison of spleen size among two study groups

The baseline ferritin level was found to be comparable among the two groups, however, post intervention the mean ferritin was 3202.5 ± 225.8 ng/ml in iron chelation plus hydroxyurea group compared to 4158.4 ± 507.7 ng/ml in no hydroxyurea group. This difference was found significant between the two groups (p-value, <0.001). (Table 2) and (Figure 1& 2)

Discussion

In the present study a significant decrease in the liver and spleen size was witnessed in beta thalassaemia patients given hydroxyurea with iron chelation therapy compared to those given iron chelation alone. The role of hydroxyurea in depletion of ferritin level has been witnessed by some investigators in the region before as well.[8-11] A study in India witnessed this trend as well as a study by Alibouyeh M et al from Iran reported that hydroxyurea significantly decreased ferritin levels in cases where an overload was present before intervention.[8,9]

Hydroxyurea is a DNA antimetabolite increases stress erythropoises by increasing fetal heamoglobin (HbF). Achieving a gap of few days in transfusion every month brings marked annual reduction of transfusion and consequently infused iron through blood is also cut down. Resulting achievement of less infused ironand consequently control on hepatospleenomegaly is a major step towards better management of thalasemia. [10,11]

Iron over load has critical manifestations for liver, spleen, heart as these patients can easily develop fibrosis or later on cirrhosis, hepatic failure,hypersplenism,cardiac decompensation, endocrine complication. Thus, controlling iron overload promises a better organ functioning and maintainenceof iron level in the body.[11,12]

Though, hyper-transfusion has resulted in better life expectancy of thalassaemic patients. However, iron overload is an unavoidable complication suffered by thalassaemia major patients as a consequence of continuous blood transfusions. Some investigators call it a "second disease" during treatment of first.[12]

It has been concluded by many that liver cirrhosis hypersplenism,cardiac decompensation and endocrine complication are all co-related to increased serum ferritin levels in the body.[13] Over the recent decades, the management of thalassaemia major is improved dramatically to that extent that patients' life expectancy has much increased.[14]

These outcomes result from safer blood transfusions, the availability of three iron chelators, new imaging techniques that allow specific organ assessment of the degree of iron overload.[15] There is, therefore, a need for quantitative, non-invasive methods for measuring body iron that are safer, accurate and easily available. The overload status of iron can be assessed by different techniques i.e. laboratory investigations. Serum ferritin measurement gives one quantitative finding whereas ultrasound of liver can tell only the alteration in the normal shape and size of liver.[16]Although New technique T2* MR imaging gives more reliable concentration of liver and cardiac iron but because of non availability of these methods in our hospital we only relied only on serum Ferritin, non invasive test done from single focal laboratory.

The liver,spleen and other body organs are the major site of iron overload, containing 70% or more of body iron content. Liver iron correlates closely with total body iron in transfusional iron overload and total body iron.[17]

Beta thalassaemia is a lifelong haemopoeteic disorder, the study on these cases has many advantages for the patients and community. Iron overload is a serious side effect of transfusions in these patients and assessment of the intervention of hydroxyurea was an additional benefits for these cases and their families. Since every patient is not lucky enough to find 100% HLA matched donor. If a child is deprived of matched related donor even then he should be in optimum health for comfortable life. For bone marrow transplant iron reduction and downstaging (reduction in size of liver and spleen) is a pre requisite. Fortunately no complications related to chelation or hydroxyurea therapy was seen. The current study findings clearly differentiate the effects of hydroxyurea on the size of liver and spleen and serum ferritin levels , however, it is mandated that large scale randomized trials must be conducted to validate the results of the current study at national and international level.

Conclusion

A combination of hydroxyurea and iron chelation therapy is better than iron chelation therapy alone in controlling enlargement of spleen , and also limiting iron stores within adequate range.

References

1. Imani E, AsadiNooghabi F, Hosseini Teshnizi S. Comparison quality of life in patients with thalassemia major based on participating in group activities, Bandar Abbas. Sci J Iran Blood Transfus Organ. 2013;10(2):198-206.
2. Keshtkaran A, Javanbakht M, Salavati S. Cost-utility analysis of oral deferasirox versus infusionaldeferoxamine in transfusion-dependent betathalassemia patients. Transfusion. 2013;53(8):1722-29
3. Modell B, Darlison D. Global epidemiology of haemoglobin disorders and derived service indicators. Bull World Health Organ 2008; 86: 480-85
4. Javanbakht M, Keshtkaran A, Shabaninejad H. Comparison of blood transfusion plus chelation therapy and bone marrow transplantation in patients with β-Thalassemia: Application of SF-36, EQ-5D, and visual analogue scale measures. Int J Health Policy Manag 2015; 4(11): 733–40
5. Ministry of Health. Comprehensive guidelines and educational materials national prevention program of beta thalassemia. Tehran: Center of publishing sound; 2004
6. Melchiori L, Gardenghi S, Rivella S – Beta-Thalassemia: HiJAKing Ineffective Erythropoiesis and Iron Overload. AdvHematol. 2010; 2010:938-41
7. Pignatti CB, Galanello R. Thalassaemias and related disorders :Quantitative disorders of haemoglobin synthesis . Wintrobe's Clinical Hematology, 13th ed.862-913
8. Italia K, Jain D, Gattani S, Jijina F, Nadkarni A. Hydroxyurea in sickle cell disease, a study of clinico-pharmacological efficacy in the India haplotype. Blood Cells Mol, Dis 2009;42: 25-31.
9. Italia KY, Jijina FJ, Merchant R, Panjwani S. Response to hydroxyurea in β thalassaemia major and intermedia: experience in western India. Clin Chem. Acta 2009;407:10-15
10. Alebouyeh M, Moussavi F, Haddad-Deylami H, Vossough P. Hydroxyurea in the treatment of major β-thalassemia and importance of genetic screening. Ann Hematol 2004; 83: 430-33.
11. Fatima I, Yaqub N, Anwar T, Nisar YB, Gilani S. Prevalence of Endocrine Complications in Transfusion-Dependent Beta Thalassemic Pakistani Patients. Int J Pathol 2014; 12(2): 77-82
12. Riaz H, Riaz T, Khan MU. Serum ferritin levels, socio-demographic factors and desferrioxamine therapy in multi-transfused thalassemia major patients at a government tertiary care hospital of Karachi, Pakistan. BMC research notes 2011; 4:287-90
13. Knovich MA, Storey JA, Coffman LG. Ferritin for the clinician. Blood Rev. 2009; 23:95-104
14. Berdoukas V, Farmaki K, Carson S. – Treating thalassemia major-related iron overload: the role of deferiprone. J Blood Med. 2012; 3:119-29
15. Jensen PD. Evaluation of iron overload. Br J Haematol. 2004; 124:697- 711
16. Agarwal MB – Advances in management of thalassemia. Indian J Pediatr. 2009; 76:177-84
17. Bandyopadhyay U, Kundu D, Sinha A. Conservative management of Beta-thalassemia major cases in the sub-division level hospital of rural West Bengal, India. J Nat SciBiol Med. 2013; 4:108-12

Contribution of Authours: Tatheer Zahra=A,B,D; Wajeeha Amber=C,D; Itrat Fatima=E

Key for Contribution of Authours : A= Conception/ Study/ Designing /Planning; B= Experimentation/Study conduction;C=Analysis/Interpretation/ Discussion; D= Manuscript writing;E= Critical review;F= Facilitated for reagents/Material/Analysis