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Assessment of Iron Overload and Liver Dysfunction by Estimation of S. Ferritin and Liver Enzymes in Transfusion Dependent β-Thalassemia Patients

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ABSTRACT

Introduction: β-thalassemia is the most frequent single gene disorder in the world. As a result of repeated transfusions, significant hepatic fibrosis develops over time and its progression is directly related to degree of iron overload. In the present study we investigated the relationship between the extent of hepatocellular injury as reflected by liver function tests (LFTs) and serum ferritin.

Materials and Methods: It was an analytical cohort study carried out during the time period from January 2017 to June 2018 from High Performance Liquid Chromatography (HPLC) confirmed β-thalassemia patients, dependant on regular blood transfusion.

Results: Our study included 58 (58%) male patients and 42 (42%) female patients. Level of Hemoglobin and Packed cell volume (PCV) increased after 6 months of chelation therapy compared to pre-chelation levels. Whereas, the S. Ferritin and Liver enzymes levels decreased after 6 months of initiation of chelation therapy.

Conclusion: High S. ferritin is a sensitive predictor of hepatic dysfunction, hence, it is a good and reliable non-invasive screening test for iron overload but it is not a good indicator of disease progression, as it has low specificity above levels of 2500 ng/ml. Combination therapy with deferiprone and deferasirox is more effective than either drug alone.

Key words: β-Thalassemia, Iron Overload, S. Ferritin, Liver Enzymes.

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INTRODUCTION

Thalassemias are a group of heterogeneous heritable disorders of reduced alpha-globin or beta-globin chains of haemoglobin A (HbA).[1] It is the most frequent single gene disorder in the world.[2] The most severe form of β- thalassaemia is β- thalassaemia major, also known as Cooley's anemia.[3] It is characterized by severe anemia beginning in the first year of life. Patients require maintenance red cell transfusions every 4-6 weeks.[4]

As a result of repeated transfusions, significant hepatic fibrosis develops over time and its progression is directly related to degree of iron overload which may be attributable to hyper-transfusion, inadequate chelation, erythrocyte breakdown and, over-absorption of iron from the gut, as a consequence of ineffective erythropoiesis. Oral iron chelation therapy reduces levels of stored iron but its efficacy is limited by dose related side effects and variable response in each patient. In the present study we investigated the relationship between the extent of hepatocellular injury as reflected by serum levels of biochemical markers, liver function tests (LFTs) and iron status as reflected by serum ferritin, in transfusion dependent thalassemia patients. We also assessed efficacy of oral iron chelation therapy with Deferiprone, Deferasirox or combination therapy by its correlation with percentage of lowering of S. ferritin levels after 6 months of therapy compared to levels before the therapy commenced.

Liver biopsy and Superconducting quantum Interface Device (SQUID) or Magnetic resonance imaging (MRI) are other methods used to assess iron overload and assessing prognosis. SQUID and MRI offer the advantage of non-invasive methods in addition to the high precision and accuracy.[5]

MATERIALS AND METHODS

It was an analytical cohort study carried out during the time period from January 2017 to June 2018 from known β-thalassemia patients presenting at Zonal Blood Bank of J.L.N. Medical College, Ajmer, for blood transfusion.

Inclusion Criteria

1. Patients with confirmed diagnosis of β- thalassemia made on HPLC (High performance liquid chromatography).
2. Patients requiring red cell transfusion at regular intervals.
3. Patients taking oral iron chelation therapy for at least 6 months duration.

Exclusion Criteria

1. History of jaundice due to hepatitis B/C (viral hepatitis), alcohol or toxins.
2. Non- transfusion dependent thalassemia patients
3. Patients not taking oral iron chelation therapy or therapy for less than 6 months.

EDTA and plain serum samples were collected from 100 known beta-thalassemia patients. Tests were done to estimate haemoglobin, packed cell volume (PCV), S. ferritin, S. bilirubin, alanine amino-transaminase (ALT) and aspartate amino-transaminase (AST) levels. Pre-chelation values and values after at least 6 months of chelation therapy were compared.

RESULTS

Our study included 58 (58%) male patients and 42 (42%) female patients. With resultant male: female ratio of 1.38:1. Youngest patient included was 2 years old and oldest patient was 48 years old.

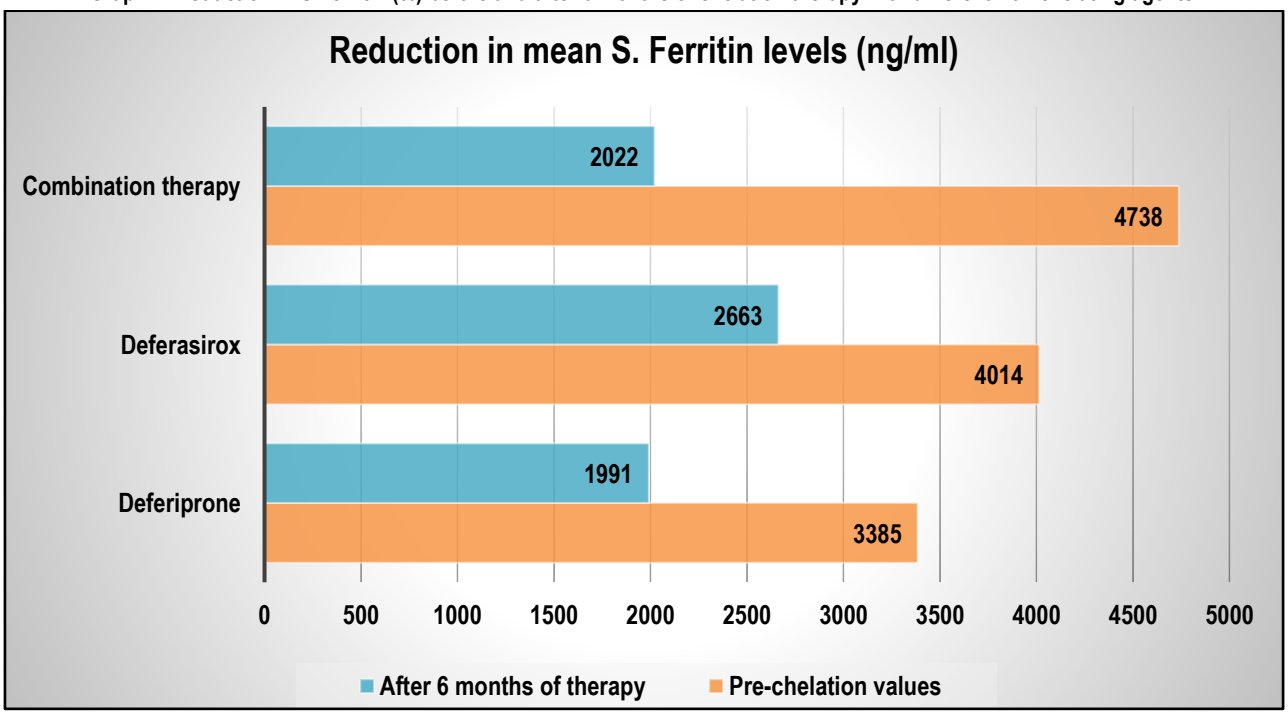
Table 1: Comparative values of blood parameters before chelation and after 6 months of beginning chelation therapy.

	Parameters	Pre-chelation values (Mean +/- SD)	Values after 6 months of chelation therapy (Mean +/- SD)
1.	Haemoglobin (g/dl)	8.05+/- 1.41	8.66 +/- 1.35
2.	Packed cell volume (%)	26.5 +/- 4.5	27.3 +/- 3.8
3.	S. Ferritin (ng/ml)	4045.67 +/- 1672.87	2225.33 +/- 1235.19
4.	AST/SGOT (U/L)	66.52 +/- 18.56	46.82 +/- 11.41
5.	ALT/SGPT (U/L)	57.28 +/- 16.71	38.76 +/- 15.58
6.	ALP (U/L)	134+/- 32.64	112.28 +/- 39.48
7.	Total S. Bilirubin (umol/L)	2.02+/- 1.12	1.32+/- 0.96

Table 2: Reduction in S. ferritin (%) before and after 6 months of chelation therapy with different iron chelating agents.

	Iron chelating agent		Range	Mean +/- SD
1.	Deferiprone	Before therapy	1072-5150	3385+/- 1200.6
		After 6 months	752-5000	1991 +/- 1010.57
		Percentage reduction of mean S. ferritin level 41.18%		
2.	Deferasiox	Before therapy	1303-10170	4014 +/- 2235
		After 6 months	1110-7240	2663 +/- 1648
		Percentage reduction of mean S. ferritin level 33.59%		
3.	Combination therapy	Before therapy	2400-7232	4738 +/- 1638
		After 6 months	885-3645	2022 +/- 1047
		Percentage reduction of mean S. ferritin level 57.32%		

Graph 1: Reduction in S. ferritin (%) before and after 6 months of chelation therapy with different iron chelating agents.



DISCUSSION

Majority of body iron is stored in form of ferritin, mostly in liver, some in spleen and bone marrow. Trace amounts of storage form is present in circulation, known as serum ferritin. Multiple transfusions at a narrow time interval leads to excessive burden of storage iron in the body. This leads to increase in the circulating levels and deposition of excess iron in the various organs. Hepatocytes are highly sensitive to free radical damage produced by accumulating iron. So, with iron overload hepatocytes are continually assaulted by reactive oxygen species and ultimately die. Damage to these cells starts to accumulate within a year of commencing transfusion therapy after as few as 10-20 transfusions. Mean pre-chelation S. ferritin level in our study was 4045.67 ng/ml, which was close to the mean values published by Arshad MS et al[6] in 2009 (mean 4718 ng/ml) and Mohammad II et al[7] in 2012 published a study with mean s. ferritin for males being 3799 ng/ml and for females being 4100 ng/ml with overall mean of 3950 ng/ml. On the contrary, Cunningham MJ et al[8] in 2004 reported a very low level of mean s. ferritin at 1696 ng/ml. And Choudhry VP[9] et al in 2006 reported very high mean levels on 6723 ng/ml. Another similar study was carried out in Jhalawar district of Rajasthan by Saral N. et al[10] where they studied liver function tests and renal function tests in relation to iron overloaded thalassemia patients compared to controls. Their mean SGPT, SGOT, ALP and bilirubin levels were 36.56+/- 22.05, 40+/-23.41, 92.26+/- 32.15 and 0.95+/- 0.62 respectively. Their results compared well with our results of patients after at least 6 months of chelation therapy.

Combining our knowledge of the subject and through this study we concluded that liver damage is augmented due to various factors including, age at diagnosis, age of first transfusion, disease progression, regular repeated blood transfusion, timeline of starting iron chelation, intolerance or dose related side-effects of iron chelating agent, damage to hepatocytes leading to reduced capacity to detoxify reactive oxygen species and self-renewal in such excess bilirubin and iron surge, secondary to hypersplenism.

CONCLUSION

High S. ferritin is a sensitive predictor of hepatic dysfunction seen in transfusion dependant β- thalassemia patients. Hence, it is a good and reliable non-invasive screening test for iron overload but it is not a good indicator of disease progression[11], as it has been found to lose specificity above levels of 2500 ng/ml.[12] Combination therapy with deferiprone and deferasirox is more effective than either drug alone. There is a definite need of developing a scoring system combining the findings of non-invasive investigations for better management of patients to reduce morbidity related to debilitating and when severe, life-threatening complications of iron-overload. Combining our knowledge of the subject and through this study we concluded that liver damage is augmented due to various factors including, increasing age with advancement of disease progression, regular repeated blood transfusion, intolerance or dose related side-effects of iron chelating agent, damage to hepatocytes leading to reduced capacity to detoxify and regenerate in such excess bilirubin and iron surge, secondary to hypersplenism.

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