

ORIGINAL ARTICLE

Study of Beta Thalassemia Major Patients with Special Reference To Iron Chelation and Cardiac Function

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ABSTRACT

BACKGROUND: Thalassemia is one of the most common monogenic disorder affecting human races. Generally an increase in body iron burden occurs in patients who are not receiving transfusions ranging from 2 to 5g/year. Iron overload cardiomyopathy is one of the common cause of death in Thalassemia major patients. **AIMS AND OBJECTIVES:** The purpose of this study is to study the cardiac abnormalities, efficacy and adverse effects of iron chelator agent- Deferasirox and to study the role of 2D echo and cardiac MRI in iron overload. **MATERIALS AND METHODS:** A prospective study of 185 patients was conducted from September 2013 to August 2015. All patients who were diagnosed as thalassemia major were included in my study and all patients > 10 years were subjected to cardiac evaluation while patients of age > 12 years, having congenital heart disease or history of cardiac surgery sickle thalassemia, haemoglobin E disease, thalassemia intermedia and other thalassemia syndromes were excluded. **OBSERVATIONS AND RESULTS:** In our present study regarding iron overload most common features were hepatomegaly and splenomegaly. Majority had their serum ferritin levels between 2500-5000µg/L. Out of 31 patients, 3 patients that got iron deposition on cardiac MRI, out of them two had normal systolic and diastolic function on ECHO. **CONCLUSION:** Serum ferritin can be used as an easily accessible serum marker for transfusion-induced iron overload. Cardiac MRI can be considered as a more sensitive indicator of cardiac iron overload than echocardiography.

Key Word: Iron overload features, Correlation between Serum ferritin and BTR, Dose Vs Response

INTRODUCTION

Thalassemia is one of the most common monogenic disorder affecting human races. It is estimated that >400,000 newborns are born with this disease worldwide. The disorder is more frequent in the subtropical and tropical areas and is very common in the Indian subcontinent.

Thalassemia major patients require intensive blood transfusions due to severe anemia from ineffective erythropoiesis. Generally an increase in body iron burden occurs in patients who are not receiving transfusions ranging from 2 to 5g/year, compared with 0.0015g/year in healthy individuals. Regular blood transfusions

may double this rate of iron accumulation. Hence the inevitably pursuant complications are from iron excess in various organs such as the liver, heart and pancreas mainly. Although the heart is not the first target organ, cardiac iron overload or iron overload cardiomyopathy is regarded as the most serious condition. Despite the advances in the management, cardiac complications still remain the major cause of mortality and morbidity in these patients unless detected and treated early.

AIMS AND OBJECTIVES

- To study the clinical features of iron overload and its impact on growth in Thalassemia major patients.
- To establish the role of serum ferritin as a marker of iron overload
- To study the 2D Echo Abnormalities and role of Cardiac MRI in Thalassemia major patients.
- To study the efficacy and adverse effects of iron chelator agent- Deferasirox.

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MATERIALS AND METHODS

A Prospective study of 185 patients was conducted from September 2013 to August 2015 at B.J. Medical College and Civil hospital, Ahmedabad

Inclusion criteria:

- All patients who were diagnosed as thalassemia major in our institute
- All patients eligible were put on oral iron chelating agent- deferasirox.
- For cardiac evaluation: all patients > 10 years were subjected.

Exclusion criteria:

- Patients of sickle thalassemia, hemoglobin E disease, thalassemia intermedia and other thalassemia syndromes.
- Patients having congenital heart disease or history of any type of cardiac surgery.
- Age > 12 years.

Methods:

- All the patients were diagnosed using hemoglobin electrophoresis.
- Moderate transfusion regimen was practised where the pre transfusion hemoglobin was maintained between 9 - 10 gm/dl as it gives a near physiological oxygenation.
- All the patients in my study were transfused with leucodepleted ABO and Rh (D) compatible packed red blood cells after screening of transfusion transmitted infections.
- Volume per transfusion usually given was 10-15 ml/kg administered over three to four hours.
- Serial monitoring of serum ferritin as a marker of iron overload was done in all patients every 3 monthly to monitor the efficacy of iron chelation.
- Chelation therapy with deferasirox was started when (whichever was earlier)
 - 1.Serum ferritin persistently > 1000 ng/ml
 - 2.When 15 transfusions have been given
- All patients needing chelation therapy were started on deferasirox. Initial dose was 15mg/kg and increased upto 45mg/kg as per requirement.
- For cardiac evaluation
 - 1.All patients with age 10-12 years were subjected to ECG, Chest X-ray,

Echocardiography and Cardiac MRI to detect iron overload cardiomyopathy at the earliest sign.

- 2.Echocardiographic Abnormalities were noted
- 3.Comparison of serum ferritin, echo findings and cardiac MRI findings were done in view of iron overload.

OBSERVATIONS AND RESULTS

In our study maximum number of the patients belonged to age group 4-6 years, 59 out of 185 which come out to be 31.89%. Sex incidence was 2.1:1 with male predominance.

In our present study clinical evaluation regarding iron overload revealed hepatomegaly in 71.89% and splenomegaly in 69.72%. Skin pigmentation was due to iron deposition in skin seen in 38.9% of the patients.Short stature was seen in nearly 22.7% of the patients in our study.Incidence of thalassemicfacies (28.1%) has been low in our study as majority of the patients are well transfused keeping their pre-transfusion Hb not less than 9.5gm/dl.

42 patients out of 185 have height < 3rd percentile i.e nearly 22.7%.Majority of these were above 7 years.Patients having weight < 3rd centile are 34 out of 185 which comes out to be 18.37%.

In our study, majority (38.91%) had their serum ferritin levels between 2500-5000µg/L while only 5.4% had very high ferritin levels > 7500µg/L.As shown in the group having serum ferritin levels < 2500µg/L majority (67.6%) had their Annual BTR < 140ml/kg/yr. While in the group having serum ferritin > 7500µg/L around 70% had their Annual BTR > 220 ml/kg/year.

50% of the patients with short stature had their serum ferritin levels between 5000-7500.

In our study 163 out of 185 patients are on deferasirox which comes out to be 88.1%.

In our present study 123 out of 163 patients were responders to deferasirox by showing a decreasing trend of serum ferritin levels. This comes out to be 75.46%.Response was maximum in the dose range of 26-40 mg/kg/day.

The most common deferasirox related adverse effects were elevated serum creatinine levels (29.44%) followed by transient gastrointestinal disturbances (22%). These increases in serum creatinine were sometimes transient and generally within the normal range, and they never exceeded 2 times the ULN

Raised SGPT levels were found in only 11.65% and rashes in around 10.42%. All these adverse events were mild to moderate in severity. No serious or life threatening events were noted.

A total of 31 patients in the age group range of 10 to 12 years underwent a detailed echocardiography examination. All the patients had normal systolic and diastolic function by and large except one. In our study only 3 out of 31 patients (9.67%) showed cardiac iron deposition when subjected to cardiac MRI. One patient had reduced ejection fraction. In the three patients that got iron deposition on cardiac MRI, out of them two had normal systolic and diastolic function on ECHO whereas one patient had reduced ejection fraction on ECHO also.

Table 1: Signs and Symptoms of Iron Overload

Signs/symptoms	No. Of patients	Percentage of Present study	Girinath et al	De Sanctis et al
Hepatomegaly	133	71.89%	88%	-
Splenomegaly	129	69.72%	82%	-
Skin pigmentation	72	38.9%	36%	-
Thalassemicfacies	52	28.1%	74%	-
Growth retardation	42	22.7%	-	35%

Chart 1:

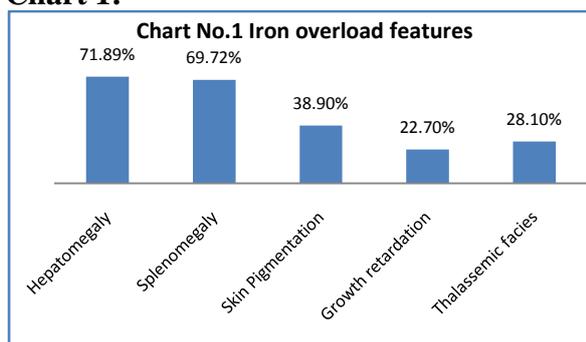


Chart 2:

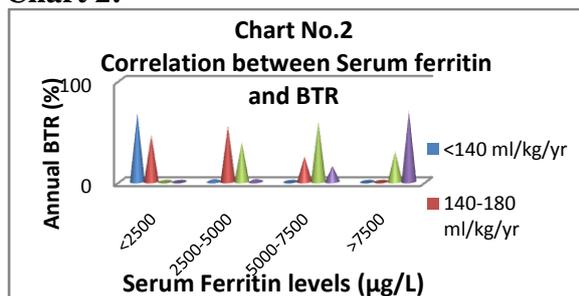


Table 2: Correlation Between Serum Ferritin and Growth Retardation

Serum ferritin (µg/L)	No. of patients with growth retardation (height<3 rd centile) (n=42)
<2500	-
2500-5000	15 (35.7%)
5000-7500	21 (50%)
>7500	6 (14.28%)

Table 3: Efficacy of Deferasirox as A Chelator Agent: By Relative Change in Serum Ferritin Levels

Dose of deferasirox	Response to deferasirox: change in serum ferritin levels		
	Decrease	No change/increase	Total
15-25 mg/kg/day	42 (25.76%)	21	63
25-40 mg/kg/day	55 (33.74%)	11	66
≥40 mg/kg/day	26 (15.95%)	8	34
Total	123 (75.46%)	40	163

Chart 3:

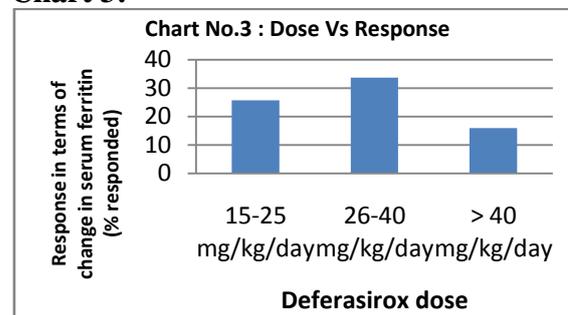


Table 4: Adverse Effects of Deferasirox

Adverse event	No. of patients (n=163)
Mild elevation in serum creatinine	48 (29.44%)
Transient GI disturbances	36 (22%)
Abdominal pain	14 (8.58%)
Nausea/vomiting	12 (7.36%)
Diarrhoea	10 (6.1%)
Raised SGPT levels	19 (11.65%)
Rashes	17 (10.42%)

Table 5: Correlation Between Echocardiography And Cardiac Mri

Positive Cardiac MRI results (n=3)	Echocardiography results	
	Normal systolic and diastolic function	Reduced ejection fraction
2	2	1

In our present study clinical evaluation regarding iron overload revealed hepatomegaly in 71.89%, splenomegaly in 69.72%, Skin pigmentation due to iron deposition in 38.9% of the patients. This is comparable to Girinath et al study. Short stature was seen in nearly 22.7% of the patients in our study. Incidence of thalassemicfacies (28.1%) has been low in our study as majority of the patients are well transfused keeping their pre-transfusion Hb not less than 9.5gm/dl. In the present study growth retardation

became pronounced with increasing age which is in agreement with these studies (Borgna- Pignati et al.1985; Kattamis et al.1990; Karagiorga- Lagana et al.1980; Pantelakis et al.1973, 1993). According to Saxena et al. it showed that patients of thalassemia major who are treated with frequent transfusions and chelation therapy, grow normally up to the age of 8-11 years, but thereafter show growth retardation most often coupled with delay in sexual maturation. Our study is comparable to this. It was seen that height is more affected than weight. Hence stunting is far more common than wasting; thalassemia being a chronic disorder. Stunted growth occurs mainly due to chronic anemia, transfusion related iron toxicity, hypersplenism, chronic malnutrition, chronic liver disease, psychosocial stress etc. In our study, majority (38.91%) had their serum ferritin levels between 2500-5000 μ g/L while only 5.4% had very high ferritin levels > 7500 μ g/L. It was also observed that high serum ferritin levels were more common with increasing age probably due to iron overload with increasing number of blood transfusions per year with age. Serum ferritin has been extensively used as an easily accessible serum marker for transfusion-induced iron overload. The major drawbacks of ferritin are a lack of specificity and interpatient variability. Inflammation, disseminated malignancy, and chronic diseases can also cause large amounts of ferritin to be released in the circulation, making a single elevated reading unreliable. However in our study we have taken serial readings of serum ferritin for better prediction of iron overload. In our study it was seen that there was a positive correlation between the serum ferritin levels and the annual blood transfusion requirement. Negative correlation was observed between serum ferritin levels and height. This is comparable to other studies where there were similar findings- Hashemi et al, Moayeri et al and Shalini S et al. Thus proving that high serum ferritin levels during the first decade of life predicts final short stature. "Serum ferritin level thus can

be a predictor of impaired growth and in thalassemia major patients". In our present study 123 out of 163 patients were responders to deferasirox by showing a decreasing trend of serum ferritin levels. This comes out to be 75.46%. Response was maximum in the dose range of 26-40 mg/kg/day. Poor compliance was one major factor responsible in the group not responding to deferasirox in our study. This is comparable to Porter et al 72.7% had a serum ferritin response and 27.3% had no response.

A total of 31 patients in the age group range of 10 to 12 years underwent a detailed echocardiography examination. All the patients had normal systolic and diastolic function by and large except one had reduced ejection fraction. Increased left ventricular end diastolic diameter was seen in 9.67%. Decrease in deceleration time seen in 6.45% of patients.

In comparison even Valdez-Cruz et al, Favilli et al observed that there was an increase of the Left ventricular end diastolic diameter (LVDD). Consequently, as far as the systolic function of the left ventricle is concerned, it is apparent in our study as well as in other previous studies, that despite regular chelation therapy there is still an increase of the LVDD as an early symptom of the cardiac involvement.

In our study we had lower percentages of pathological indices of the left ventricle diastolic function (6.45%), in comparison to earlier studies. Our findings were attributed to the younger ages of our patients and to the regular regimen of blood transfusions and chelation therapy.

Only seeing for the presence of systolic or diastolic function will not help because that will be affected in only advanced stage of iron deposition. (Aessopos et al)

Thus Echocardiography is a noninvasive screening method, easily available, safe and economical and should be a part of regular cardiac monitoring of patients.

In our study only 3 out of 31 patients (9.67%) showed cardiac iron deposition when subjected to cardiac MRI. One patient had reduced ejection fraction. According to M. BARZIN et al study most of the iron loaded patient is in

the age of 15-40 y/o according to their life expectancy and duration of blood transfusion. And similarly John C Wood et al study found cardiac iron in 8/10 patients older than 13 years of age and 0/9 patients under 13 years of age. In both these studies comparable to ours all patients were well chelated and on a regular transfusion regimen.

Three patients who developed cardiac iron overload had their serum ferritin > 7500 µg/dl secondary to irregular follow up and poor compliance. Not all patients who had their serum ferritin > 7500 had cardiac involvement showing that we also cannot exclude the potential role for maturational, hormonal, or nutritional changes with age and genetic factors in facilitating cardiac iron uptake.

Thus as early as ten years cardiac involvement can be seen if patients are not well chelated. Majority of them being well chelated in our centre have not developed cardiac iron overload.

In the three patients that got iron deposition on cardiac MRI, out of them two had normal systolic and diastolic function on ECHO whereas one patient had reduced ejection fraction on ECHO also. Cardiac MRI can be considered as a more sensitive indicator of cardiac iron overload than echocardiography. Again the sample size being so small for comparison we cannot come to a proper conclusion neither could we draw a correlation between serum ferritin and positive cardiac MRI results.

However studies like M. BARZIN et al suggest that in equipped centres where Cardiac MRI is available it should be the first examination in high risk patients and regular follow up with echocardiographic evaluation with detailed parameters.

CONCLUSION

With increasing age annual blood transfusion rate increases and hence the iron overload increases. A careful watch should be kept on the clinical features of iron overload. Serial serum ferritin can be used as a surrogate marker for early detection of iron overload. In view of cardiac function Cardiac MRI can be considered as a more sensitive indicator of

cardiac iron overload than echocardiography. In equipped centres where Cardiac MRI is available it should be the first examination in high risk patients above ten years and regular follow up be done with echocardiographic evaluation with detailed parameters.

LIMITATIONS

The sample size being so small for comparison we cannot come to a proper conclusion neither could we draw a correlation between serum ferritin and positive cardiac MRI results. Hence the results need to be further validated.

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