

## A study conducted in a tertiary care hospital to assess the cardiac function in paediatric beta thalassemia major patients and correlation with serum ferritin levels which are indicative of chelation status of the patients

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### ABSTRACT

**Background:** Thalassemia is one of the common inherited blood disorders and Beta Thalassemia Major is a homozygous form of deficiency of beta globin chain synthesis causing severe transfusion-dependent anemia, manifesting between 6 and 24 months of life.

**Objectives:** The objective of the study is to study the pattern of cardiac function in children and adolescents with beta-thalassemia major by 2D Echocardiography and its correlation with serum ferritin levels. **Methods:** Fifty subjects diagnosed with Beta Thalassemia Major, after applying the inclusion and exclusion criteria were included in Group 1, and 50 age and gender-matched subjects without Beta Thalassemia Major were included in Group 2. Serum ferritin level was measured using Cobas 6000 analyzer. Echocardiography was done with the following parameters: Posterior wall thickness-diastolic (PWT-D), posterior wall thickness- systolic (PWT-S), left ventricular internal diameter-diastole (LVID-D), left ventricular internal diameter-systole (LVID-S), septal thickness and tricuspid regurgitation (TR) velocity. **Results:** Among the 50 study population, 28 children belonged to the age group 5–10 years (56%) and 22 children belonged to the age group 10–15 years (44%). Among the cardiac parameters, The PWT-D, PWT-S, LVID-D, LVID-S, TR velocity, and septal thickness values were higher in the cases group compared to the control group with p values suggesting strong significance. The ejection fraction in the cases was lower than the control group with a strongly significant p-value. **Conclusion:** Children with thalassemia have impaired cardiac function and the degree of dysfunction is correlated to the serum ferritin levels. Regular transfusion and adequate chelation are essential to decrease morbidity and mortality.

**Key words:** Blood transfusion, Echocardiography, Beta thalassemia major, Chelation Therapy


Thalassemia is one of the most common inherited disorders of the blood [1], which arises from a decreased or absent synthesis of the globin chain part of hemoglobin. Thalassemia is inherited in an autosomal recessive manner and is a quantitative defect of hemoglobin synthesis. Beta Thalassemia refers to an inherited mutation of the beta-globin gene, which causes decreased synthesis of the beta-globin chain of hemoglobin. Thalassemia major is a homozygous form of deficiency of beta globin chain synthesis which results in severe transfusion-dependent anemia, which usually becomes apparent between 6 and 24 months of life. It is estimated that all over the world, there are 200 million carriers of the beta thalassemia gene, of which about 40 million are in South Asia and 20 million of them are in India alone.

The two important factors which contribute to the sequelae of Beta thalassemia syndromes are inadequate beta globin gene

production leading to decreased levels of normal hemoglobin and an imbalance between alpha and beta globin chains leading to ineffective erythropoiesis. Hematopoietic stem cell transplantation is the curative treatment for beta thalassemia major [2] with regular blood transfusions (BTs) in the interval period, usually administered every 2–5 weeks, to maintain the pre-transfusion hemoglobin level above 9–10.5 g/dL. Iron overload happens when iron intake is increased over a prolonged period. In beta thalassemia major, iron overload occurs as a result of regular BTs and also due to increased absorption of iron through the gastrointestinal tract. It is initially deposited in the liver and is followed by deposition in the endocrine organs and the heart. Iron deposition in the heart can lead to complications like heart failure, arrhythmias, and arterial changes. Iron chelation therapy should start as soon as the patient becomes significantly iron-overloaded to prevent such complications. In general, this occurs after 1 year of transfusion therapy and correlates with the serum ferritin of >1000 ng/mL and/or a liver iron concentration of >5000 ug/g

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dry weight [3]. Cardiac iron accumulation is one of the biggest risk factors for cardiac dysfunction in thalassemia. Cardiac iron loading occurs when the heart is subjected to high circulating non-transferrin-bound iron species for a prolonged time. Iron excess can affect the pericardium, myocardium, valves, and conduction tissue, resulting in a variety of symptoms such as arrhythmia, diastolic dysfunction, systolic dysfunction, pleural effusion, pericardial effusion, ascites, peripheral edema, and other signs of cardiac failure. Numerous parameters can be obtained from the cardiac ultrasound investigation but the simplest measurements of chamber size provide immediate and significant data on cardiac status and clinical progress.

Our study aims to identify the extent of cardiac dysfunction among children and adolescents by 2D echocardiography and the correlation with serum ferritin levels.

## MATERIALS AND METHODS

A hospital-based cross-sectional study was conducted involving 50 children with beta thalassemia major and 50 healthy (control) children. All enrolled children were subjected to detailed clinical history including age at first BT, number of BT, duration of iron chelation therapy, and general physical examination findings which were recorded on a predesigned pro forma. Before BT, for all enrolled beta Thalassemia major children, after informed consent from the parents of the children, one blood sample was sent for serum ferritin level and another sample for pre-transfusion Haemoglobin. Serum ferritin level was measured using Cobas 6000 analyzer.

Echocardiography was done with the following parameters for comparison with Serum Ferritin: Posterior wall thickness-diastolic (PWT-D), posterior wall thickness-systolic (PWT-S), left ventricular internal diastolic diameter (LVID-D), left ventricular internal systolic diameter (LVID-S), and septal thickness. Tricuspid regurgitation (TR) and pulmonary insufficiency jets provide estimates of pulmonary artery systolic and diastolic pressure, respectively. TR velocity below 2.5 m/s represents a negative screening test, 2.5–3.0 m/s a borderline finding, and TR velocity >3 m/s a positive finding.

## Statistical Analysis

All the statistical analysis was carried out using Statistical Program for Social Science statistical package for Windows (version 17). Descriptive statistics such as mean, standard deviation, frequency, and percentage were used. Inferential statistics will include a chi-square test to test the differences in proportions and an independent sample t-test, will be used for comparison of the two groups. A  $p < 0.05$  will be considered significant.

## RESULTS

In our study, we divided the children into two age groups according to the inclusion criteria of 5–15 years. The two age

groups were 5–10 years and 10–15 years. Among the cases, it was found that a greater proportion of children belonged to the age group of 5–10 years that is 28 children with the percentage being 56. The other group of children (who belonged to the age group of 10–15 years) consisted of the rest 44% i.e., 22 children. In our study, the mean age among cases was 9.84 years.

In the control group, there were 26 in the age group 5–10 years (52%) and 24 in the 10–15 years (48%). The mean age in the control group was 10.08 years. Female children consisted of 23, which made up 46%. Male child predominance was found in this study, with the total number of male children being 27 (54%). This was the same in the control group also.

The average mean weight was 26.9 kg while in the control group, it was 32.98 kg. The p-value was 0.002 which is strongly significant for this study. Similarly, the average mean height was 127.2 cm, and in the control group, it was 137.58 cm with a strongly significant p-value of 0.002. The body mass index was 15.71 kg/m<sup>2</sup> and in the control group, it was 16.85 kg/m<sup>2</sup> p-value was 0.036 which shows moderate significance (Table 1).

In 54% of the cases, the age at which it was diagnosed was >1 year, while 46% were diagnosed with the illness when they were less than a year old suggesting the early presentation of the disease.

Fig. 1 shows that with an increase in the average number of transfusions per year, there is a corresponding increase in the serum ferritin levels.

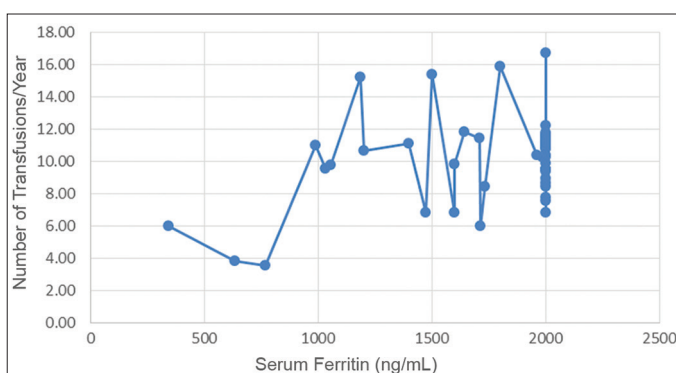
Fig. 2 shows that with an increase in age, there was a corresponding increase in the number of transfusions.

The minimum age of diagnosis was 0.3 years (4 months) and the maximum was 5 years with a mean of 1.355 and a Standard deviation of 1.068. The minimum number of transfusions was 26 and the maximum was 260 with a mean of 115.98 and a

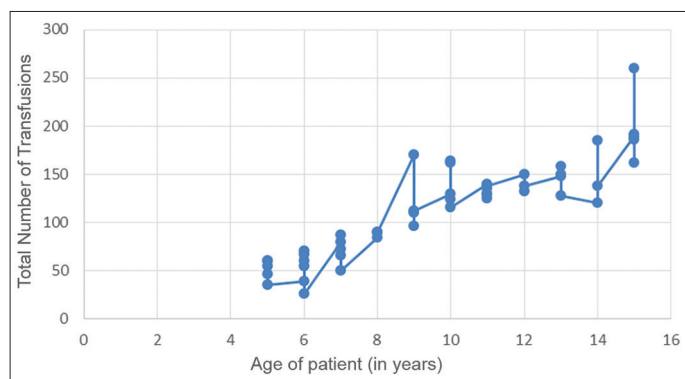
**Table 1: Comparison of weight, height, and BMI in two groups of patients studied**

Variables	Cases	Control	Total	p-value
Weight	26.36±9.6	32.98±11.09	29.67±10.84	0.002**
Height	127.2±16.42	137.58±15.56	132.39±16.75	0.002**
BMI	15.71±2.51	16.85±2.86	16.28±2.74	0.036*

\*\*Strongly significant. \*Moderately significant. BMI: Body mass index



**Figure 1: Comparing the number of transfusions per year with serum ferritin levels**



**Figure 2: Comparing the number of transfusions with the age of patients**

Standard deviation of 50.616. The average/transfusions per year had a minimum of 3.57 and a maximum of 16.733 with a mean of 10.129 and a standard deviation of 2.609. The minimum HB recorded was 5 and the maximum was 9 with a mean of 7.58 and a standard deviation of 0.928. The Minimum Ferritin was 343 and the maximum was 2000 with a mean of 1746.34 and a standard deviation of 421.25 (Table 2). In 94% of the cases (47 in number) underwent chelation therapy while only 6% amounting to 3 cases did not undergo chelation therapy.

The PWT-D was 0.53 cm while in the control group, it was 0.44 cm. The p-value was 0.003 suggesting strong significance. The PWT-S was 0.61 while in the control group, it was 0.49. The p-value was <0.001 suggesting strong significance. LVID-D was 3.91 while in the control group, it was 2.73. The p-value was <0.001 suggesting strong significance. The LVID was 2.42 while in the control group, it was 1.79. The p-value was <0.001 suggesting strong significance. The TR velocity was 2.42±0.25 whereas, in the control group, it was 2.04±0.24 with a p value of <0.001 suggesting strong significance. The septal thickness was 6.01±1.01 and in the control group, it was 4.84±0.5 with a p value of <0.001 suggesting strong significance (Table 3). The ejection fraction in the cases was 63.42±5.17% while in the control group, it was 68.12±2.5% with a strongly significant p-value of ≤0.001.

## DISCUSSION

During the study period, 72 children came for regular BTs. After applying filters for age, diagnosis, and consent, 50 children in the age group 5–15 years satisfied the inclusion-exclusion criteria.

Among the cases, it was found that a greater proportion of children belonged to the age group of 5–10 years that is 28 children (56%). In our study, the mean age among cases was 9.84 years. The mean age in the control group was 10.08 years.

Male child predominance was found in this study, with the total number of male children being 27 (54%) and female children being 23 (46%). In Indian literature, a male preponderance of up to 68% [4] and 69.5% [5] has been reported. It could probably be due to gender inequality in the health-seeking behavior for chronic illnesses. In 54% of the cases, the age at which it was diagnosed was >1 year, while 46% were diagnosed with the illness when

**Table 2: Descriptive statistics**

Variables	Minimum	Maximum	Mean	Standard deviation
Age at diagnosis (years)	0.300	5.000	1.355	1.068
Number of transfusions	26.000	260.000	115.980	50.616
Average transfusions/year	3.571	16.733	10.129	2.609
HB	5.000	9.000	7.580	0.928
Ferritin	343.000	2000.000	1746.340	421.254

**Table 3: Comparison of 2D echocardiography parameters in the cases and control group**

Variables	Cases	Control	Total	p-value
PWT-D (cm)	0.53±0.18	0.44±0.07	0.48±0.14	0.003**
PWT-S	0.61±0.21	0.49±0.09	0.55±0.17	<0.001**
LVID-D	3.91±0.48	2.73±0.54	3.32±0.78	<0.001**
LVID-S	2.42±0.5	1.79±0.43	2.1±0.56	<0.001**
TR velocity	2.42±0.25	2.04±0.24	2.23±0.31	<0.001**
Septal thickness (mm)	6.01±1.01	4.84±0.5	5.42±0.99	<0.001**

\*\*Strongly significant. PWT-D: Posterior wall thickness-diastolic, PWT-S: Posterior wall thickness-systolic, LVID-D: Left ventricular internal diastolic diameter, LVID-S: Left ventricular internal systolic diameter, TR: Tricuspid regurgitation

they were less than a year old suggesting the early presentation of the disease. The mean age of presentation was 1.35±1.06 years.

The minimum haemoglobin recorded was 5 and the maximum was 9 with a mean of 7.58. In another study based in Mangalore [6], the mean baseline hemoglobin value was 7.3 ± 1.7 g/dL which is comparable to our study and the mean post-transfusion level of hemoglobin was 10 g/dL indicating appropriate transfusion practices as per guidelines [7]. It is recommended that the hemoglobin level is maintained at more than 9–10.5 g/dL [8].

The minimum ferritin was 343 and the maximum was 2000 with a mean of 1746.34 and a standard deviation of 421.25. In 94% of the cases (47 in number) underwent while only 6% amounting to 3 cases did not undergo chelation therapy. The cardiac parameters were evaluated by 2D echocardiography. In our study, there was strong statistical significance for PWT-D, PWT-S, LVID-D, LVID-S, ejection fraction, TR velocity, and septal thickness as seen by other studies by Shivaswamy *et al.* [9], Noori *et al.* [10], Lau *et al.* [11], Sayed *et al.*, [12] as well. The TR Velocity in our study was 2.42±0.25 and studies by Mohammad *et al.* [13] suggest that a TR velocity >2.5 is suggestive of pulmonary hypertension. Shivanna *et al.* [14] in their study “Cardiac abnormalities in children with thalassemia major: Correlation of echocardiographic parameters with serum ferritin levels”, a prospective study done in 2015 on 30 cases of Thalassemia major attending a tertiary referral center for a period of 2 years found that Serum Ferritin levels were higher (2610±115.33) in patients who had received more than 50 transfusions. Echo parameters were compared; an increase in LVESD was noted in cases when compared to statistically significant controls (0.006).

The limitation of our study was that it was a small-sized study and serum ferritin levels in our hospital could not be estimated beyond 2000 ng/mL. The strength of our study was that an age and gender-matched case-control study was designed.

## CONCLUSION

In children with thalassemia even after significant toxic effects of iron on heart muscle have prevailed, aggressive iron chelation can restore myocardial function to normality. Serum Ferritin levels are an indicator of the chelation status and echocardiographic findings are significantly altered in patients with poor chelation status. Hence, regular transfusion along with adequate chelation and annual screening for other organ involvement are necessary to reduce the burden of the disease and improve the quality of life.

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