Original Article

Myocardial performance index in children with β-thalassemia major

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ABSTRACT

Background: Cardiac complications are the major cause of mortality and morbidity in thalassemic children. Iron deposition in myocardium is the key factor leading to poor cardiac functions. Myocardial performance index (MPI) by echocardiography (ECHO) can be used for an early recognition of ventricular dysfunctions. **Objectives:** To assess the MPI in children with β-thalassemia major and to establish their relationship with serum ferritin. **Methods**: Fifty-five children of Thalassemia major in age group of 4-20 years who were on regular blood transfusion and on oral iron chelators from thalassemia unit of tertiary hospital were enrolled. After blood transfusion, serum ferritin estimation was done. Two dimensional ECHO with color Doppler was done to estimate the cardiac functions and then MPI by various parameters was calculated. **Results:** Out of 55 children, most were in the age group of 4 to 8 years. Mean rate of blood transfusion in subjects was 157.01 ± 21.33 ml/kg/year and mean duration of chelation therapy was 2.34 ± 1.86 years. Mean serum ferritin of subjects was 2130 ± 859.5 ng/ml. Mean ejection fraction was 61 ± 6.2%. Mean MPI of subjects was 0.60 ± 0.14. The MPI was abnormal at all levels of more than 1000 ng/ml serum ferritin (p=0.001). There was a positive correlation between MPI and serum ferritin (Pearson's bivariate correlation coefficient r=+0.93). **Conclusion:** In poorly chelated thalassemic children, MPI was abnormally high despite normal ejection fraction, which can be used as an early marker of ventricular dysfunction.

Key words: *β-thalassemia major, Echocardiography, Myocardial performance index, Serum ferritin*

β-thalassemia major is an autosomal recessive disorder seen all over the world caused by defect in β-globin chain synthesis of hemoglobin. In individuals with thalassemia, there is either complete absence of β-globin production (β-thalassemia major) or partial reduction of β-chain synthesis (β-thalassemia minor). Thalassemia gene is carried by 150 million or 3% of the world population with clinically apparent disease only in 15 million populations. One lakh thalassemic children are born every year in world and 10000 In India [1,2].

Cardiac complications are the major cause of mortality and morbidity in these children. Heart failure is responsible for 71% deaths in thalassemia major in United Kingdom. In response to iron loading, human myocytes upregulate the transport of non-transferrin bound iron; thus, aggravating the cardiac iron loading [3]. Extensive iron deposition is associated with increase in cardiac stiffness; thus, elevating the left ventricular (LV) and right ventricular (RV) diastolic pressure followed by reduction in the cardiac contractility in later stages [4]. Patient is considered to have heart disease in the presence of any one of the followings is present - LV ejection fraction (LVEF) <60%, persistent arrhythmias, pulmonary artery hypertension, and pericarditis [5].

Endomyocardial biopsy is the gold standard for assessing cardiac iron overload [5] and T2 magnetic resonance imaging (MRI) is the best noninvasive method for evaluating cardiac iron in early stages [6]. As T2-MRI is expensive and available at very limited centers, the 2D Echocardiography (ECHO) is the easiest available diagnostic technique for the diagnosis of cardiac dysfunction. Features that are seen in Echo are - high cardiac output, diastolic dysfunction, chamber enlargement, increase in LV mass and volume, decreased LVEF. Tissue Doppler ECHO has been recently used to evaluate early myocardial dysfunction in adult patients with Thalassemia [7].

Myocardial performance index (MPI) is an easier method to assess heart functions. The index is a Doppler derived time interval index that combines both systolic and diastolic cardiac performance. This is also called as Tei index, which is easily derived using conventional pulsed Doppler and M-mode views recorded at 50 mm/s velocity [8,9]. This study was conducted to assess the MPI and serum ferritin in children with β-thalassemia major and to establish their relationship.

METHODS

The study was single centre tertiary hospital based prospective correlation study carried out in thalassemia unit of Balchikitsalaya, MB Hospital of RNT Medical College. The study was conducted between January 2015 and November 2015. Institutional Ethical Committee permission was sought

and written consent was taken from parents of children before recruiting into the study. A total of 86 children were on roll in our thalassemia ward. We included those children who were of more than 4 years of age, on regular blood transfusion and chelation therapy (deferasirox) for at least one year. Children who were in congestive cardiac failure at the time of study were excluded from the study. All children were transfusion dependent at the rate of once or twice a month. These children were seronegative for HIV, HCV, and HbsAg and were not having any other significant medical or surgical co-morbidity.

In present study, children more than 4 years were included as in younger children it is difficult to know the cardiac dimensions, velocities, and timing of various cardiac cycles because of relatively small size of cardiac chambers and tachycardia in younger ones. After routine blood transfusion, 2 ml of venous blood was taken for hemoglobin and serum ferritin estimation. Serum ferritin was measured by Elecys 2010 which uses ferritin specific antibody sandwich principle and takes 18 min. Sample passes through two faces in which two different ferritin specific antibody coats the ferritin.

2D ECHO was performed with a challenger 7000 ECHO machine with a 3.5/5 and 2.5/3.5 MHZ transducer. Patient's recording was taken while patient in supine position without breath holding. 2D and Doppler echocardiographic measurements were taken and averaged over 3 cycles. Pulsed Doppler method was used for blood flow measurement from cardiac valves. Flow velocity during early filling (E), flow velocity during atrial contraction (A), ejection time (ET), isometric relaxation time (IRT), and isometric contraction time (ICT) were obtained from apical five chamber view.

MPI was measured according to formula[8]: MPI = IRT + ICT/ET. MPI >0.36 was taken as abnormal which indicates impairment in either systolic or diastolic heart functions. Higher value indicates poorer ventricular function.

Results were correlated and statistical analysis was done using Pearson's bivariate coefficient test. All data analysis was done by SPSS version 16 statistical software.

RESULTS

Fifty-five thalassemic children of 4-20 year age group who fulfilled the inclusion criteria were finally enrolled. Out of them, majority (60%) of children were in age group of 4-8 year. Only 14.54% children were more than 12-years-old. Female preponderance in subjects (56.4%) was seen. Most of the patients belonged to Hindu religion (87.3%) and the rest were Muslims. Mean Hb concentration after blood transfusion was 9.7 g/dl. All basic parameters of subjects were as shown in Table 1.

Twenty-three (41.81%) children had serum ferritin concentration in between 1000-2000 ng/ml and mean serum ferritin level was 2130 ± 859.5 ng/ml. Only 5% children maintained serum ferritin below 1000 ng/ml. MPI at different level of serum ferritin is shown in Table 2. Different echocardiographic variables were as shown in Table 3. The mean MPI was 0.60 ± 0.14 which was highly abnormal as compared to normal value of <0.36. When MPI was correlated with serum ferritin it has positive correlation, MPI worsens with increase in serum ferritin (Pearson's bivariate correlation coefficient, r=+0.93). MPI becomes >0.36 as serum ferritin crosses 1000 ng/ml (p=0.001) as shown in Fig. 1.

When Echocardiographic variables were correlated with serum ferritin as shown in Fig. 2, there was positive correlation between ICT, IRT with ferritin (i.e., ICT and IRT increases as ferritin increases), and negative correlation between ET and ferritin (i.e., ET decreases as ferritin increases). Pearson's bivariate correlation coefficient (r=+0.91, r=+0.88, and r=−0.87), respectively. When MPI was correlated with number of blood transfusions, MPI becomes abnormal (>0.36) when it exceeds 30 in most of the children and it further increases with increase in number of blood transfusions. However, there was not much increase in MPI after 100 transfusions as depicted in Fig. 3.

DISCUSSION

Our study shows that serum ferritin levels were highly increased in thalassemic children. Thalassemia is secondary iron overload

Table 1: Basic general variables in thalassemic children

Variables	Mean±SD
Age (years)	8.8±3.88
Age at diagnosis (in months)	29.90±31.04
No. of blood transfusions	84.65±85.71
Rate of blood transfusion (ml/kg/year)	157.01±21.33
Dose of deferasirox (in mg/kg/day)	34.4±26.86
Duration of chelation therapy (in years)	2.34±1.86

SD: Standard deviation

Table 2: Distribution of thalassemic children according to their serum ferritin and MPI

Serum ferritin (in ng/ml)	Number of children (%)	MPI Mean±SD	p
<1000	3 (5.45)	0.38±0.14	0.8
1000-2000	23 (41.81)	0.50±0.14	0.001
2000-3000	20 (36.36)	0.64±0.13	0.001
>3000	9 (16.36)	0.81±0.14	0.001
Total	55 (100)	0.60±0.14	0.001

SD: Standard deviation, MPI: Myocardial performance index

Table 3: Different echocardiographic variables in thalassemic children

Echocardiography variables	Mean±SD
Isovolumic contraction time (m sec)	60.9±13
Isovolumic relaxation time (m sec)	81±8.5
Ejection time (m sec)	241±21.8
Ejection fraction	61±6.2
MPI	0.60±0.14

p=0.001. SD: Standard deviation, MPI: Myocardial performance index

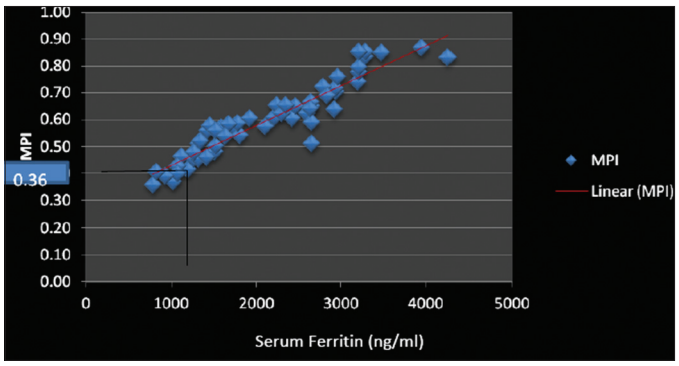

Figure 1: Correlation of myocardial performance index with serum ferritin in thalassemic children

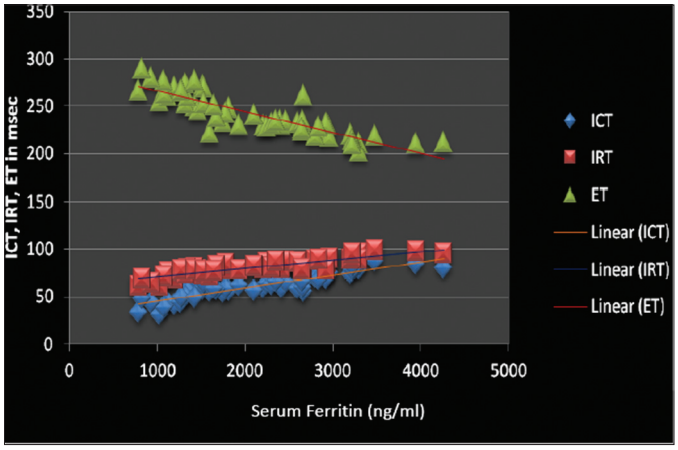

Figure 2: Correlation of isovolumic contraction time (ICT), isovolumic relaxation time (IRT) and ejection time of left ventricle with serum ferritin level in thalassemic children

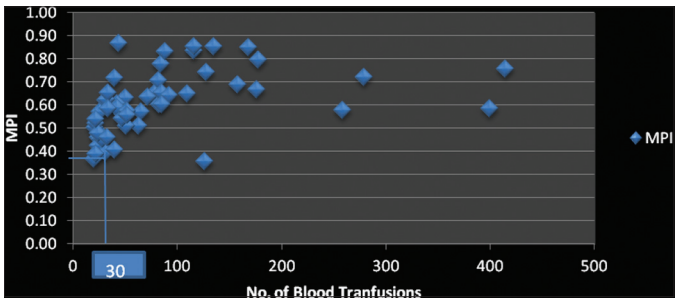

Figure 3: Correlation of myocardial performance index with Number of blood transfusions in thalassemic children

state. This iron overload is due to frequent blood transfusions (as shown by positive correlation between number of blood transfusions and serum ferritin, r=+0.33). This high level also suggests that these patients were poorly chelated.

In present study, we studied cardiac systolic and diastolic functions of both the ventricles but for practical purposes highlighted only of left ventricle in thalassemic children. MPI was highly abnormal when compared with normal values in children in spite of normal ejection fraction. IRT and ICT were significantly raised (correlation coefficient, r=+0.91, r=+0.88), while ET was reduced (r=−0.87), when correlated with increasing serum ferritin levels. This finally describes the worsening of MPI with increase in serum ferritin (r=+0.93).

MPI is independent of arterial pressure, heart rate, ventricular geometry, atrioventricular valvular regurgitation, and pre and after load; thus, it is a useful diagnostic tool for assessing cardiac functions in children with thalassemia major [8].

Ocal et al. in 2006 studied MPI of left heart in chemotherapy patients and found that it helps in identifying cardiac complications of cancer therapy such as LV systolic and diastolic dysfunctions [10]. Gharzuddine et al. conducted a study on cardiac and pulmonary dysfunction in 26 asymptomatic β-thalassemia major patients and observed that right and left ventricular MPI in study group were significantly different from controls. These findings showed that systolic and diastolic dysfunctions were present in β-thalassemia [11]. Borzoee and Kheirandish found that right and left ventricular MPI were 0.25 ± 0.09 and 0.36 ± 0.11, respectively [12]. Siddammanahalli et al. in their study showed that MPI becomes abnormal after serum ferritin level crosses 1000 ng/ml and it increases with increasing ferritin levels [13].

Javier et al. conducted a meta-analysis where several echocardiographic parameters were chosen and analyzed in comparison with cardiac MRI findings to detect myocardial iron overload in thalassemia patients who undergo regular blood transfusion. Tissue Doppler parameters that were seen to have good correlation with the current gold standard were Tei index, DT, and LVEF. In our country, where cardiac MRI is available in only a few institutions and carries a significant burden of cost, these tissue Doppler indices may be used as screening parameters to detect early myocardial iron overload, especially in asymptomatic patients. Significant findings in these studies may likewise be used for monitoring the course of these patients, including their response to iron chelation therapy. However, these parameters were compared only to cardiac MRI which is still the gold standard in the detection and quantification of myocardial iron loading [14].

Uçar et al. evaluated the left and right ventricular MPI using pulsed-tissue Doppler imaging (TDI) and its relation to β-natriuretic peptide (BNP) levels in patients with β-thalassaemia major. All the patients' plasma BNP levels were within normal limits, and there were no differences between conventional echocardiographic parameters of the patient and control group. MPI of LV, IVS, and RV of patients were significantly higher than the control group ($p=0.01$, and $p<0.01$, and $p<0.001$, respectively). They concluded that MPI obtained by TDI may be an adjunctive parameter to conventional ECHO for detecting early myocardial damage [15].

Our study results were comparable to other studies depicting the role of MPI in assessing the ventricular functions and higher values of MPI indicate worse myocardial performance. Limitation of our study was that we did not include controls which could have given better comparative results.

CONCLUSION

Our study shows that MPI is abnormal in iron overloaded thalassemic children and it increases as serum ferritin and number

of transfusions increases. Hence, the screening of the heart with ECHO and assessing MPI for ventricular dysfunction should be started as soon as the number of blood transfusions crosses 30 or serum ferritin level exceeds 1000 ng/ml in thalassemic children.

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