Original Article

Study of echocardiography in thalassemia (major/intermedia) patients at tertiary care center

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ABSTRACT

Objective: The objective of this study is to study the cardiovascular complications and to establish the role of echocardiography (ECHO) screening in beta thalassemia major (TM) and intermedia patients, aged 2–12 years, receiving one or more transfusions per month for 2 or more years. **Methods:** A cross-sectional study was done at tertiary care center from June 2015 to November 2015. Hemoglobin, serum ferritin, and 2D ECHO were done before the blood transfusion. **Results:** Male preponderance was seen with a ratio of 1.7:1. 87% (n=47) had TM and remaining had thalassemia intermedia (TI). Serum ferritin in TM was >1000 ng/ml in 80.9% (n=38) of cases and <1000 ng/ml in 19% (n=9) of cases. Serum ferritin in TI was above 1000 ng/ml in 42.8% (n=3) and <1000 ng/ml in 57.14% (n=4) of cases. 64% (n=35) had cardiomegaly in X-ray. 2D Echo showed increased LV mass in 71.1% (n=27) of cases and normal LV mass in 28.9% (n=11) of cases. Pulmonary hypertension was seen in 21.2% (n=10) of cases of TM and 42% (n=3) of cases with TI. **Conclusion:** ECHO combined with electrocardiogram should be used for regular periodic monitoring of transfusion-dependent thalassemia patients.

Key words: *Cardiomyopathy, Left ventricular dysfunction, Pulmonary hypertension, Thalassemia,*

Anemia is the decrease in total circulating erythrocytes below the normal cutoff for the corresponding age, race, and sex [1,2]. Anemia has a high prevalence in Asian and African countries, whereas thalassemia is the most common hemolytic anemia worldwide [3-5]. Mutations of β globin genes occur predominantly in children of Mediterranean, Southern, and South East Asian ancestry [2]. Prevalence is high in Punjab and Sindhis in North India [4,6].

Frequent blood transfusion to mainatin desired hemoglobin often leads to depoistion of iron in vital organs such as heart, liver, lung spleen and endocrine glands. As a result, complications such as growth retardation, endocrine disturbances, and osteoporosis occur [7-10]. Cardiac complications are the most common cause of death in thalassemia patients. Cardiomyopathy occurs due to chronic anemia and tissue hypoxia [11]. The American Heart Association consensus statement on the cardiovascular function and treatment in β thalassemia major (TM) patients states that the most common cause of mortality in transfused patients of TM is heart failure due to iron overload [12]. The pathology in thalassemia is not only the hemolysis and iron overload but also the adaptation of the heart to the long-standing anemia. Symptoms of chronic anemia, breathlessness, and exercise intolerance mask the clinical diagnosis of failure. Cardiac adaptations to chronic anemia such as tachycardia at rest, low blood pressure, increased end-diastolic volume, increased ejection fraction, and high cardiac output may delay the diagnosis [13,14].

Increased incidence of pulmonary hypertension (PH) and arrhythmia is seen in these patients compared to the general population. PH is defined as a mean pulmonary artery pressure of 25 mmHg or above in an individual at rest at the sea level [15]. This chain of anemia, hypoxia, vasoconstriction, endothelial injury, hypercoagulability, free radical injury, proliferation of smooth muscles, and obliteration of pulmonary vasculature recurs many times in thalassemia patients which ultimately causes PH [16,17]. Free radical injury due to iron in the lungs is also postulated as a possibility for the development of PH by immunoinflammatory pathway.

Diagnosis of PH in thalassemia patients requires regular and periodic screening as the majority of them are asymptomatic. Before the advent of iron chelating therapy, chronic severe anemia and iron overload were the primary causes for cardiomyopathy and mortality in thalassemia [14]. With the introduction of blood transfusions and chelation therapy, the morbidity and deaths have been pushed a decade later. Clinically alone, it is difficult to pick up symptoms of heart failure as symptoms of anemia overlap. Hence, these patients need continuous monitoring of symptoms and signs aided with investigations for the early detection of complications and its management for better outcome.

To detect this pre-symptomatic stage of cardiac complications, many techniques are available such as electrocardiogram (ECG), echocardiography (2D ECHO), T_2-cardiac magnetic resonance

imaging (MRI), and Multigated Acquisition Scanning. ECG and ECHO are cost-effective, non-invasive, and easily available; however, the gold standard to assess the cardiac iron overload is done by MRI which is expensive. Disadvantage includes high cost, time consumption, non-availability in resource-poor settings, claustrophobia, contraindicated in patients with cardiac pacemaker, metallic fragments and requires highly skilled personnel for the procedure [17]. In India, studies regarding the screening of cardiac complication in the first decade in thalassemia cases by ECHO are not available so far. Studies from the Middle East have shown that ECHO can be used to detect cardiac dysfunction before clinical symptoms and sign appear [17-19]. The objective of this study was to evaluate the role of non-invasive ECHO as a screening tool for the detection of cardiac complications in thalassemia patients who are on regular blood transfusion.

METHODS

This study was conducted in a pediatric hospital in Chennai from June 2015 to November 2015. A total of 54 β-thalassemia patients between 2 and 12 years of age, who were on regular blood transfusion, were included in the study. Children with congenital heart disease and those with the terminal illness were excluded from the stduy. The Institute Ethical Committee clearance was taken, and after obtaining consent from the parents, demographic and anthropometry for body mass index (BMI), clinical history involving the family history, and transfusion details were taken. Investigations, complete blood count, chest X-ray, serum ferritin using chemiluminescence technology, ECG, and ECHO were done. Doppler ECHO was done as per the guidelines of the American Society of ECHO.

Left ventricular (LV) end-diastolic dimension (LVEDD), LV end-systolic dimension (LVESD), systolic and diastolic interventricular septum thickness (IST), and LV posterior wall thickness in systole and diastole were calculated using M-mode ECHO. Ejection fraction and fractional shortening were also calculated using the same. LV mass was calculated using the formula 0.8×1.04×(LVEDD+posterior wall thickness + IST) 3-(LVEDD) 3) +0.6, and LV mass index was indexed to body surface area. Tricuspid regurgitant (TR) velocity was measured by pulsed Doppler. PH was measured using TR jet velocity and modified Bernoulli equation (ΔP=4V2). These results were tabulated using charts (ECHO in pediatric and congenital heart disease, Wiley–Blackwell, Oxford [UK] 2010 for LV dimension, and wall thickness) [15]. LV mass and LV mass index by M-mode ECHO was calculated by the above formula and tabulated as per the percentile charts [15].

Appropriate statistical analysis for means, standard deviations, Fisher's exact test, and coefficient of correction values was calculated with 95% confidence intervals, p value at 5% significance ($p<0.05$) using SPSS 21.

RESULTS

In our study, 54 children were selected, 34 (63%) were <6 years, and 20 (37%) were between 6 and 12 years of age. 57% of them were from rural areas with slight male preponderance (63%). 24 (44 %) children were born to consanguineous parents. 3rd month was the earliest age of the diagnosis with mean age of diagnosis of 9 months. 47 (87%) of them were of TM and 7 (13%) of intermedia. In spite of being on oral chelators, 41 (76%) had serum ferritin >1000 ng/ml and only 13 (24%) had <1000 ng/ml. Patient with least value of 215 ng/ml had thalassemia intermedia (TI), on transfusions once in 3 months. 4 of 7 TI patients had ferritin <1000 ng/ml and 3 of them had higher values. Patients with low values of ferritin had an average of a total of 30 transfusions. Of the 47 TM patients, 9 (19%) had serum ferritin values <1000 ng/ml, whereas 38 (80.90%) had >1000 ng/ml (Table 1).

The ECG results showed that, of the 38 TM patients with high ferritin values, 8.5% had right ventricular hypertrophy (RVH) on ECG. Serum ferritin had no association with LV hypertrophy (LVH) in ECG. 36% (17) of TM had LVH in ECG. QTc interval was normal in all patients, and no arrhythmia was noted. Of 47 TM patients, 32 (67%) had abnormal ECHO findings. Of 38 TM patients with elevated serum ferritin level, 27 (71.1%) had increased LV mass/m^2 and 11 (28.9%) cases had normal LV mass despite increased serum ferritin level. 3 TM patients with serum ferritin <1000 ng/dl had increased LV mass ($p=0.034$) as shown in Table 1.

There was a poor positive correlation between LV mass and TR velocity ($p=0.06$) and poor negative correlation between EF and TRV ($p=0.477$). It indicates that right and LV dysfunction can occur independently. In our study, 3 (42%) TI patients and 10 (21%) TM patients had PH, which showed that the incidence of PH was more common in TI than in TM. 8 (62%) of 13 children with PH were diagnosed as thalassemia in their infancy ($p=0.019$). Mean hemoglobin in patients with PH was 7. 33±1.13 g, and the mean age was 5.38 years. A total of 10 (21.2%) TM children with PH had serum ferritin >1000 ng/dl, but PH and serum ferritin had no association ($p=0.148$). 25 TM patients had TR, but there was no association with serum ferritin levels ($p=0.623$) as shown in Table 1.

The sensitivity of ECHO in comparison with ECG, in the detection of any cardiac complication in thalassemia patient on chronic blood transfusion, was 89.47% and specificity was 45.71%. The negative predictive value of echo was 88.89% as shown in Table 2.

DISCUSSION

Patients in the majority of the previous studies conducted to assess the cardiovascular complications included patients >10 years of age. In our study, 63% were <6 years and 37% between 6 and 12 years. In studies by Sayed *et al*. [18] and Noori *et al*. [19], all the patients were more than 10 years of age and Azarkeivan *et al*. [20] had patients >7 years of age. It was seen in these studies that cardiac complications occur early in spite of regular blood transfusions and in well-chelated patients.

In our study, 29 (54%) patients had tachycardia, and mean hemoglobin in these patients was 7.33±1.13 g/dl; mean EF was

Table 1: Demographic and clinical factors and relation with serum ferritin levels

Parameters	n (%)	p
Age	<6 years - 63% (n=34) 6–12 years - 37% (n=20)	
Sex	Male - 63% (34) and female - 37% (20)	
Residence	Rural - 57% (31) and urban - 43% (23)	
Type	TM - 47 and TI - 7	
Frequency of transfusion	TM - 87% (47) - once per month TI - 9% (5) - once in 2 months	
Malnourished	33%	
Heart rate	Normal - 46% (n=25) Tachycardia - 54% (n=29)	
Mean hemoglobin	7.33±1.13 g%	
Serum ferritin	>1000 ng/ml - 76% (n=41) <1000 ng/ml - 24% (n=13)	
TI serum ferritin	>1000 ng/ml - 42.8% (n=3) <1000 ng/ml - 57.14% (n=4)	
TM serum ferritin	>1000 ng/ml - 80.9% (n=38) <1000 ng/ml -19% (n=9)	
Serum ferritin and Consanguinity	Consanguineous - 24 Non-consanguineous - 30	p=0.413, df=1
Serum ferritin and residence	Rural - 31 and urban – 23	p=0.504, df=1
ECG	RVH - 8.5% LVH - 36%	P=0.756, df=1 p=0217, df=1
ECHO	Mean ejection fraction - 69.96%	SD 5.637±0.767
Serum Ferritin with LV mass	Increased 63% (34) Normal 37% (20)	Pearson correlation 0.064
LV mass on Echo (T major)	Increased - 71.1% (n=27) Normal - 28.9% (n=11)	p=0.034, df=1
Ejection Fraction	69.96±0.767	
Pulmonary artery pressure	Increased - 24% (n=13) Normal - 76% (n=41)	p=0.019, df=1
PH	TM - 21.2% (n=10) TI - 42% (n=3)	
PH and serum ferritin >1000	21.2 (n=10)	p=0.148, df=1

RVH: Right ventricular hypertrophy, LVH: Right ventricular hypertrophy, TM: Thalassemia major, TI: Thalassemia intermedia, PH: Pulmonary hypertension

Table 2: Wilson score method

Parameter	Estimate (%)	Lower–Upper 95% CIs
Sensitivity	89.47	(68.61, 97.06[1])
Specificity	45.71	(30.47, 61.81[1])
Positive predictive value	47.22	(31.99, 62.99[1])
Negative predictive value	88.89	(67.2, 96.9[1])
Diagnostic accuracy	61.11	(47.79, 72.96[1])

CI: Confidence interval. [1]p≤0.05

70% and fractional shortening was 39.54. Mean LVMI in these patients was 79.63 g/m^2. Similar results were seen in studies done by Sayed *et al*. [18] and Noori *et al*. [19]. All patients in this study had normal blood pressure for their corresponding age and sex. A study by Malik *et al*. [11] observed that even patients with PH had normal systemic blood pressure. In spite of being on oral chelators, 76% of the study population had serum ferritin >1000 ng/ml as compared to Samira *et al*. [18] study who had all patient with ferritin >1000 ng/ml.

In our study, no association was found with serum ferritin and ECG findings of RVH and LVH. In our study, 35 (64%) had cardiomegaly on chest X-ray, but 27 (77%) of these patients had high serum ferritin values which imply that cardiomegaly in these patients can be due to chronic anemia and volume overload rather than iron overload alone. Arrhythmia was not seen in this study in contrast to Sayed *et al*. [18] where corrected QT and QT dispersion intervals were increased significantly in patients with serum ferritin >5000 ng/ml. Ejection fraction was found to be mildly elevated than the normal values for age with mean of 69.96% in the present study, which was comparable to results of other studies by Sayed *et al*. [18] (66.28%), Mohammad [21] (65%), and Azarkeivan *et a*l. [20] (60%). There was a poor negative correlation between EF and TR velocity. It indicates that right and LV dysfunction can occur independently.

LV mass and LV mass index were increased in 34 (63%) patients, and similar findings were observed in studies done by Noori *et al*. [19], Abbas *et al*. [22], Mosa *et al*. [21], and Sayed *et al*. [18]. Increase in LV mass and LV mass index in thalassemia is multifactorial. It is due to chronic anemia, tissue hypoxia, and iron overload, and there was a poor positive correlation between LV mass and TR velocity.

PH was seen in 24% in our study, wherein 10 (21%) TM and 3 (42%) TI patients had PH. All 10 had serum ferritin >1000 ng/ml which shows that PH was more in TI than in TM. Sylvia *et al*. [23] also observed that high prevalence of PH is seen in well-transfused TM patients and most importantly in TI patients. A total of 8 (62%) of 13 children with PH were diagnosed to have thalassemia in their infancy; the incidence of PH showed significant association with the age of diagnosis (p=0.019). This implies that incidence of PH in TI is high as the age advances; however, it had no association with consanguinity, geographical distribution, or sex of the patient. In a study by Meloni *et al.* [24], it was seen that, well tnanfused TM paitents had low risk of PH than TI. Sylvia *et al*. [17] also had a high prevalence of PH in TI. These patients also had low hemoglobin and high serum ferritin than those who did not have PH.

The sensitivity and specificity of ECHO on thalassemia patients in our study, when compared to ECG, were found to be 89.47% and 45.7%, respectively. Negative predictive value was 89%. Serum ferritin had a poor positive correlation with LV mass and PH; hence, it cannot be used as single marker for cardiac iron load in transfusion-dependent thalassemia patients. The limitation of this study was the ECHO findings which were not compared with T2* MRI which is the gold standard in the diagnosis of cardiac iron deposition, and the efficacy of this procedure in confirming cardiac iron load is less [24]. Further, PH should also be confirmed by cardiac catheterization.

CONCLUSION

Our study adds that 2D echo can be used to detect the cardiac complication in thalassemia in pre-symptomatic stage. Complications can be detected early in asymptomatic children by easily available, affordable, and non-invasive technique like ECHO.

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