International Journal of Contemporary Pediatrics
Vithalani MP et al. Int J Contemp Pediatr. 2023 May;10(5):691-696
http://www.ijpediatrics.com
pISSN 2349-3283 | eISSN 2349-3291

DOI: https://dx.doi.org/10.18203/2349-3291.ijcp20231145

Original Research Article

Evaluation of diastolic dysfunction in multi-transfused thalassemia patients

Mitsu P. Vithalani, Bhadresh R. Vyas*, Namrata Makvana

Department of Pediatrics, M. P. Shah Government Medical College, Jamnagar, Gujarat, India

Received: 10 March 2023
Revised: 07 April 2023
Accepted: 12 April 2023

***Correspondence:**
Dr. Bhadresh R. Vyas,
E-mail: vithalanimitsu@yahoo.in

ABSTRACT

Background: An important complication of thalassemia is iron deposition in the cardiac tissue resulting in degeneration, fibrosis and dysfunction. Cardiac disease is the primary cause of death. Aims and objectives were to detect early cardiac involvement in patients with transfusion dependent thalassemia by conventional doppler echocardiography and tissue doppler imaging while they are still asymptomatic.
Methods: 150 patients in the age group of 2-18 years who were receiving regular and frequent blood transfusions were enrolled in this study. Institutional ethical clearance was taken. After informed consent, 2D echocardiography was performed on all the patients. Previous blood reports reviewed. Various parameters like mitral flow pattern, LVEF and Tricuspid regurgitant jets were taken into account to diagnose cardiac dysfunction. Results analysed by standard statistical tests.
Results: Out of 150 patients, 58% were males and 42% were female patients. The 13 (8.6%) patients were diagnosed as having diastolic dysfunction. Out of 150, majority (86.6%) were below the age of 15 years, 81.33% children were diagnosed as having thalassemia before the age of 2 years, 97% patients were on regular iron chelation therapy, 32% patients had pre-transfusion Hb <7 gm/dl, 78.66% patients had S. ferritin levels >2500 ng/ml and more number of males (7.33%) have undergone splenectomy than females.
Conclusions: Diastolic dysfunction on Doppler echocardiography is an early sign of myocardial dysfunction in patients with beta thalassemia.

Keywords: Thalassemia, Diastolic dysfunction, Echocardiography

INTRODUCTION

Thalassemia is among the most common genetic disorder (Haemoglobinopathies) worldwide. Thalassemia is characterized by decreased synthesis of one of the two main globin chains (α and β chains) that are needed for the formation of normal adult haemoglobin tetramers. α or β thalassemia results depending on the globin chain synthesis i.e., defective and decreased. In India, β Thalassemia is prevalent across the country, with an average frequency of carriers being 3-4%.[1]

β thalassemias are clinically divided into thalassemia major (TM), thalassemia intermedia (TI) and thalassemia minor or trait according to severity. TM and TI constitute major burden of disease as management of both requires lifelong blood transfusions and iron chelation.

An important complication of β-TM is iron deposition in the cardiac tissue resulting in degeneration, fibrosis and dysfunction. Ozment et al suggested that 10-15 ml/kg of packed cell RBCs transfusion will lead to approximately 250 mg iron overload.[2] Our body can't excrete more than1 mg iron per day.

Cardiac disease is the primary cause of death.[3] Aggressive iron chelation therapy may prevent, delay or even reverse myocardial dysfunction, but once overt heart failure is present, only 50% of patients survive. The goal therefore is to begin treatment while the cardiomyopathy is still reversible.

In clinical practice, S. ferritin has been used to assess the effectiveness in treatment. Quantifying myocardial iron content has only recently become possible using magnetic resonance imaging (MRI). Cardiac T2* MRI is gold standard to detect cardiac iron overload.[4,5] However, MRI is not widely available and is time consuming and expensive. This will limit the application of this technique especially in developing countries where thalassemia is more common.

Echocardiography is more widely available. Wall motion abnormalities may represent an early sign of cardiac disease despite preserved global function. The regional abnormalities related to iron overload are easily detectable with echocardiography. Intensive chelation therapy can restore normal cardiac function in patients with pre-clinical dysfunction and in some cases of frank cardiac failure.

This study is done to assess echocardiographic findings in thalassemia patients.

Aim

Aim of the study was to detect the early cardiac involvement in patients with β-thalassemia.

Objectives

Objectives of the study were to assess cardiac status in patients with transfusion dependent thalassemia by conventional doppler echocardiography and tissue doppler imaging, to evaluate cardiac functions and myocardial perfusion in multi-transfused thalassemia patients while they are still asymptomatic and early detection of cardiac complications with easily available tools to improve survival in thalassemia patients.

METHODS

Study design

The present prospective study was conducted over a period of 2 years i.e., November, 2018 to October, 2020. A total of 150 thalassemia patients (age group of 2-18 years), who are taking regular and frequent blood transfusions at GG Hospital, Jamnagar, during study period, were enrolled in this study.

Type of study

Type of study was of observational, cross sectional study.

Inclusion criteria

Multi transfused thalassemia patients attending thalassemia clinic in thalassemia ward without congenital heart disease and patients of age group 2 to 18 years and patients with thalassemia who were on regular blood transfusions, irrespective of chelation were included in the study.

Exclusion criteria

Patients with less than 2 years and more than 18 years of age and parents/guardians not willing to enrol the child or to provide their voluntary written informed consent were excluded from the study.

Sampling and data collection

Prior to the conduct of the study, written approval from institutional ethical committee was taken. Convenience sampling was used to select study subjects. History including age at diagnosis, anthropometry, transfusion history, drug history, splenectomy, blood investigations and family history were noted in a pro-forma. Echocardiography done in all patients by a pediatrician who is trained for functional echocardiography and done observer ship in echocardiography.

Two-dimensional (2D) conventional, pulse Doppler transthoracic echocardiography was performed with Kontron KM 60 7393.

The LV global systolic function was evaluated via the modified biplane Simpson method for calculating the left ventricular ejection fraction (LVEF) by measuring the end-diastolic and end-systolic volumes via M Mode in the 2D images. Valvular diseases left and right atrial areas and volumes were evaluated via the apical four-chamber view. Transmittal flow patterns were obtained by pulsed-wave doppler echocardiography from apical four-chamber view. There are two flow waves in the AV (Atrial-ventricular) valves; the E wave and the A wave. The E wave occurs during the early diastolic filling phase, and the A wave occurs during atrial contraction. Peak early (E) and late (A) diastolic velocities, E/A ratios, E wave deceleration time (DT) and iso-volumetric relaxation time (IVRT) were measured. A Pulsed wave doppler tracing was placed at the level of basal segment of septal wall and early diastolic velocity (e') measured from apical four chamber view. As there are no standard cut off available for pediatric diastolic dysfunction, we have percolated adult guideline for diastolic dysfunction with modification.

Statistical analysis

All statistical calculations were assessed using SPSS software version 21. Paired 't' test was used for comparing means between the two groups.

RESULTS

In present study, a total of 150 children suffering from Thalassemia were chosen from 2-18 years of age. Study and screening to detect diastolic dysfunction by Echocardiography was done in all subjects during the period from November, 2018 to October, 2020. Observation and results are discussed as under.

Majority (86.67%) of the patients were below the age of 15 years (Table 1). A total of 87 (58%) males and 63 females (42%) were studied (Figure 1). Most of the children (81.33%) were diagnosed as having TM before the age of 2 years. As present study was conducted at government hospital, majority of the TM patients enrolled are from lower socio-economic class (84%) (Table 2). 146 out of 150 patients were on regular iron chelation therapy. There is no statistically significant difference between type of Thalassemia and blood investigations like pre BT Hb, S. ferritin, S. creatinine (Table 3).

There is statistically significant difference between E/A ratio, E/e', TR velocity and LA volume index of those patients with diastolic dysfunction and those with normal echo findings. LVEF was found within normal range in almost all the cases (Table 4).

Table 1: Age distribution.

Age (Years)	N	Percentage (%)
4-10	73	48.67
10-15	57	38.00
15-18	20	13.33
Total	150	100

Table 2: Socio-demographic details.

Class	Male	Female	N	Percentages (%)
Upper	1	0	1	0.67
Upper middle	2	1	3	2.00
Lower middle	11	9	20	13.33
Upper lower	2	0	2	1.34
Lower	71	53	124	82.66
Total	87	63	150	100

Table 3: Blood investigations.

Blood investigations	Type of thalassemia	N	Mean	SD	T value	P value
Pre BT Hb	TI	10	8.00	1.13	0.63	0.52
	TM	140	7.74	1.25		
S. Ferritin	TI	10	2912.05	1702.95	-1.90	0.06
	TM	140	4381.18	2395.68		
S. Creatinine	TI	10	0.62	0.28	1.32	0.45
	TM	140	0.54	0.15		
SGPT	TI	10	38.86	23.79	2.17	0.03
	TM	140	73.52	49.99		

Table 4: Echo findings of thalassemia patients.

Echo findings		No	Mean	SD	T value	P value
E/A ratio	N	137	1.93	0.70	-2.56	0.01
	DD	13	2.44	0.61		
e' peak velocity	N	137	16.06	10.31	1.22	0.22
	DD	13	12.39	2.17		
E/e'	N	137	6.94	1.45	-7.18	0.0001
	DD	13	10.17	1.91		
TR velocity	N	137	138.7	51.58	-4.67	0.0001
	DD	13	207.94	44.01		
LA volume index	N	137	20.21	7.91	-3.50	0.001
	DD	13	28.25	7.85		
LVEF	N	137	68.5	7.94	-1.35	0.18
	DD	13	71.9	6.19		

Out of these 5 parameters, patients with 3 or more parameters with abnormal deviation are considered as having diastolic dysfunction and accordingly 13 (8.6%) patients are showing diastolic dysfunction. The result of

diastolic dysfunction in our study (8.6%) is comparable with the prevalence reported by Kremastinos et al (7.9%).[6]

This prevalence is low as compared to previous study done by Chinprateep et al that showed prevalence of LVDD was 20.7%.[7]

The 30 (20%) out of 150 patients are showing E-A ratio > 2.26 (80th centile of mean E-A ratio) which is suggestive of restrictive left ventricular filling pattern. The 30 (20%) patients had e' peak velocity <13.04 cm/sec (20th centile for mean e' peak velocity). The 29 (19.34%) patients had E-e' septal ratio >8.21 (80th centile for mean E-e' ratio). The 30 (20%) patients had TR velocity >194.66 cm/sec (80th centile for mean TR velocity). The 30 (20%) patients had LA volume index > 24.48 ml/m^2 (80th centile for mean LA volume index) (Figure 2).

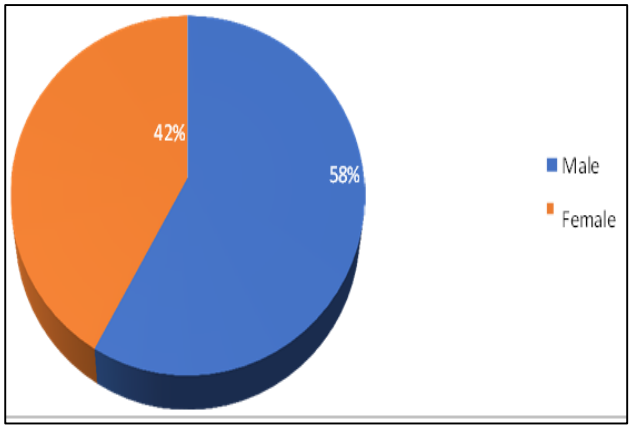

Figure 1: Gender distribution.

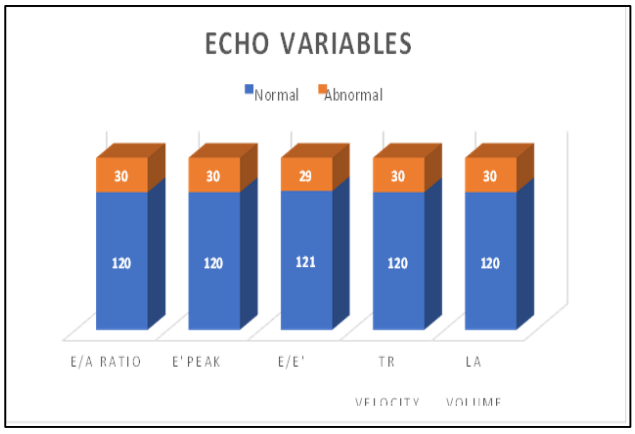

Figure 2: Echo variables.

Left ventricular diastolic dysfunction was defined as abnormal relaxation or restrictive filling pattern. All these 13 patients were considered to have DD as they were having 3 out 5 parameters abnormal. LVEF in all these patients were within the normal range i.e., 60-80% all patients had normal systolic function (Table 4).

All the patients with diastolic dysfunction had pre-transfusion Hb<9 gm/dl which is comparable with the reported study by Chate et al.[8] There is significant association between Pre-BT Hb and diastolic dysfunction (p<0.05) (Table 5).

Out of these 13 patients, youngest age observed was 4.5 years and the oldest one was of 15.5 years of age. All the 13 patients with cardiac dysfunction were males. Mean Body surface area was 0.88 m^2 and all the patients were under-weight with Mean BMI 14.68 kg/m^2.

The 12 out of 13 patients were on regular iron chelation therapy. Borgna- Pignatti et al study reported that in beta TM, transfusions and iron chelation therapy have significantly improved the survival and reduced the morbidity.[9]

The diastolic dysfunction is found significantly more in patients with S. ferritin levels >2500 ng/ml in our study which is in accordance with the results of the study conducted by Sayed et al (Table 6).[10]

Mean BT requirement of these patients was around 229 ml/kg/year, 4 out of 13 patients operated for splenectomy.

Three out of 13 were HCV reactive and 1 patient was S. RVD positive. 10 out of 13 patients had S. ferritin level >2000 ng/ml. 5 out of 13 patients had SGPT levels <40 IU/litre and 8 out of 13 patients had SGPT in the range of 40-200 IU/L.

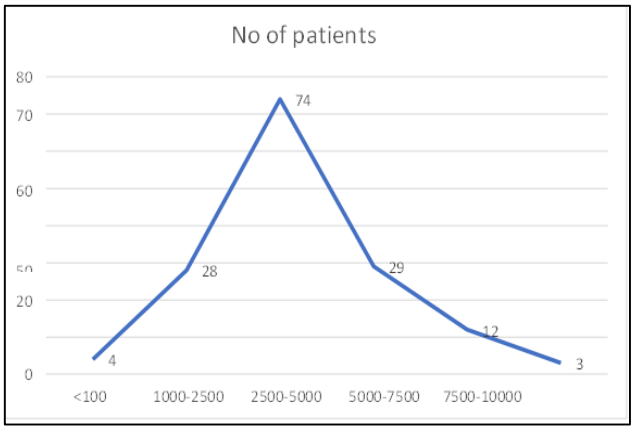

Figure 3: S. Ferritin values.

Table 5: Co-eelation of diastolic dysfunction and pre-BT Hb: comparison.

Pre-transfusion Hb	Presence of diastolic dysfunction, n (%)	
	Present study	**Chate et al study[22]**
<9	13 (8.67)	13 (40.6)
>9	0	6 (18.8)
Total	13 (8.6)	19 (59.4)
P value	0.04	0.96

Chi- square=6.17, p=0.04

Table 6: Co-relation of diastolic dysfunction and S. ferritin level.

S. ferritin (ng/ml)	Presence of diastolic dysfunction, n (%)	Absence of diastolic dysfunction, n (%)	Total, n (%)
<1000	0	4 (2.67)	4 (2.67)
1000-2500	3 (2)	25 (16.67)	28 (18.67)
2500-5000	3 (2)	71 (47.33)	74 (49.33)
5000-7500	4 (2.67)	25 (16.67)	29 (19.34)
7500-10000	2 (1.33)	10 (6.66)	12 (7.99)
>10000	1 (0.67)	2 (1.33)	3 (2)
Total	13 (8.67)	137 (91.33)	150 (100)

DISCUSSION

In present study, a total of 150 children suffering from thalassemia were chosen from 2-18 years of age, the youngest patient being 4 years old and the oldest of 18 years old. Mean age of children was 10.8 years (SD=3.74 years). Sambhaji et al conducted a prospective observational study in 32 multiply transfused thalassemic patients who were > 7 years of age.[8]

A total of 87 (58%) males and 63 females (42%) were studied. Sayed et al study included 36(64%) males and 20 (36%) females.[10]

The 146 out of 150 patients were on regular iron chelation therapy. Caro et al and Aessopos et al study on cardiac status in TM suggested that cardiac dysfunction also occurred even in some cases who accepted the chelation therapy well and in some cases because of difficulty in accepting chelation treatment, which was cumbersome.[11,12] The 11 out of 150 patients had undergone splenectomy. Chinprateep et al study on prevalence of LVDD in TM patients concluded that homozygous beta thalassemia and splenectomy were strong predictors of LVDD.[7]

In our study, mean S. ferritin value was 4283.24 ng/ml (Figure 3). Bosi et al found a weak but significant correlation between left ventricular ejection fraction and serum ferritin concentration, where patients with a high ferritin concentration (>2500 ng/ml) had a lower ejection fraction than patients with a low ferritin concentration (<1000 ng/ml).[13]

In our study, diastolic dysfunction was present in 13 (8.67%) patients, of which majority 12 (8%) patients were below the age of 15 years. Sambhaji et al study shows that diastolic dysfunction/restrictive physiology on doppler echocardiography was present in 19 (59.4%) patients out of 32.[8] The result of diastolic dysfunction in our study (8.6%) is comparable with the prevalence reported by Kremastinos et al (7.9%).[8]

All the patients with diastolic dysfunction had pre-transfusion Hb<9 gm/dl which is comparable with the reported study by Chate et al.[8] There is significant association between Pre-BT Hb and diastolic dysfunction (p<0.05) (Table 5).

The diastolic dysfunction is found significantly more in patients with S. ferritin levels >2500 ng/ml. Olivieri et al reported that the cardiovascular prognosis in patients with homozygous beta thalassemia was excellent if S. ferritin was below 2500 ng/ml.[14]

Limitations

The sample size is small and this study has been done at a centre with no cardiac T2* MRI facility (which is the gold standard for detecting iron overload cardiomyopathy) available.

CONCLUSION

This study was conducted to assess the diastolic dysfunction in multi-transfused thalassemia patients in between the age of 2-18 years.

Echocardiographic assessment revealed left ventricular diastolic dysfunction in 8.6% of the total patients (n=150). Chronic serious anaemia and the siderosis related to recurrent blood transfusions to treat this anaemia are the main reasons for cardiac disease in thalassemia patients. Clinically asymptomatic patients with myocardial iron overload can be detected by echocardiographic evaluation, which may be more appropriate for developing countries with a significant population affected by thalassemia. LV diastolic dysfunction and impaired LA active emptying fraction precede LV systolic dysfunction.

Recommendations

The leading cause of mortality in thalassemia patients is iron overload cardiomyopathy. Chelation therapy should be intensified to reverse the changes of early cardiomyopathy in patients with thalassemia.

Cardiac complications can be diagnosed and managed reasonably well in time by regular cardiac screening tools. ECHO is a commonly used tool to assess systolic and diastolicfunction and should be made easily available. Facility for MRI T2* to strengthen the early diagnosis of the cardiomyopathy is desirable in prevalent districts. Early detection of cardiac disease in thalassemic children will facilitate the prolongation of life by aggressive chelation therapy. Yearly screening of all multi-transfused thalassemic children is recommended.

ACKNOWLEDGEMENTS

Author would like to thank the patients in the thalassemia ward and their parents for their co-operation in our study.

Funding: No funding sources
Conflict of interest: None declared
Ethical approval: The study was approved by the Institutional Ethics Committee

REFERENCES

1. National Health Mission (NHM). Prevention and control of hemoglobinopathies in India- Thalassemia, Sickle cell disease and other variant hemoglobins. Guidelines on Hemoglobinopathies in India, 2016.
2. Ozment CP, Turi JL. Iron overload following red blood cell transfusion and it's impact on disease severity. Biochim. Biophys. Acta. 2009;1790:694-701.
3. Mohan JC, Reddy KS. Thalassemic cardiopathy: Current concepts. Indian J Pediatr. 1984;51:383-6.
4. Quinones MA, Otto CM, Stoddard M, Waggoner A, Zoghbi WA. Doppler Quantification Task Force of the Nomenclature and Standards Committee of the American Society of Echocardiography. Recommendations for quantification of Doppler echocardiography: a report from the Doppler Quantification Task Force of the Nomenclature and Standards Committee of the American Society of Echocardiography. J Am Soc Echocardiogr. 2002;15(2):167-84.
5. Kirk P, Roughton M, Porter JB, Walker JM, Tanner MA, Patel J et al. Cardiac T2* Magnetic Resonance for Prediction of Cardiac Complications in Thalassemia Major. Circulation. 2009;120:1961-8.
6. Kremastinos DT, Tsiapras DP, Tsetsos GA. Left ventricular diastolic Doppler characteristics in beta-thalassemia major. Circulation. 1993;88:1127-35.
7. Chinprateep B, Ratanasit N, Kaolawanich Y, Karaketklang K, Saiviroonporn P, Viprakasit V et al. Prevalence of left ventricular diastolic dysfunction by cardiac magnetic resonance imaging in thalassemia major patients with normal left ventricular systolic function. BMC Cardiovascular Disorders. 2019;19:245.
8. Sambhaji CC. Cardiac abnormalities in patients with beta thalassemia. Int J Contemporary Pediatr. 2016;3(1);224-8.
9. Borgna-Pignatti C, Rugolotto S, De Stefano P, Piga A, Di Gregorio F, Gamberini MR et al. Survival and disease complications in thalassemia major. Ann N Y Acad Sci. 1998;850:227-31.
10. Sayed SZ, Aly BA, El-Hakim A, Omar SM, Amin AS. The early cardiac involvement in patients with B-thalassemia major. Egypt Heart J. 2013;65:243-9.
11. Caro JJ, Ward A, Green TC, Huybrechts K, Arana A, Wait S et al. Impact of thalassemia major on patients and their families. Acta Haematologica. 2002;107:150-7.
12. Aessopos A, Farmakis D, Hatziliami A, Fragodimitri C, Karabatsos F, Joussef J et al. Cardiac status in well-treated patients with thalassemia major. Eur J Haematol. 2004;73:359-66.
13. Bosi G, Crepaz M, Gamberini R, Fortini M, Scarcia S, Bonsante E et al. Left ventricular remodelling, and systolic and diastolic function in young adults with beta-thalassemia major: a Doppler echocardiographic assessment and correlation with haematological data. Heart. 2003;89:762-6.
14. Olivieri NF, Nathan DG, MacMillan JH, Wayne AS, Liu PP, McGee A et al. Survival in medically treated patients with homozygous beta thalassemia. N Engl J Med. 1994;331:574-8.

Cite this article as: Vithalani MP, Vyas BR, Makvana N. Evaluation of diastolic dysfunction in multi-transfused thalassemia patients. Int J Contemp Pediatr 2023;10:691-6.