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EARLY INDICATORS OF CARDIAC DYSFUNCTION IN THALASSEMIA AND THEIR CORRELATION WITH FERRITIN LEVEL BEFORE AND AFTER CHELATION THERAPY:

Cardiology

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ABSTRACT

Objective: In this study we have assessed the cardiac profile of mult transfused β and E-β thalassemia patients along with the ferritin level and studied the effects of chelation therapy on cardiac status of the patients.

Study design: 100 thalassemia patients (β thalassemia and its variants) were selected randomly and their cardiac status was assessed by 2D M mode Echo with color-Doppler. Among these patients 54 cases are chosen who have taken Deferasirox monotherapy on a regular basis and the echo was repeated in them. We have compared the cardiac status of the patients before and after chelation therapy along with the ferritin level, thus to find out the pattern of cardiac involvement and determine the role of chelation therapy.

Results: The mean PASP value is higher in E-β patients (41.51mm of Hg) compared to the other subgroups (p value <0.01). There is a positive correlation between the grade of diastolic dysfunction and ferritn level in the pre chelation phase (R^2=.33 & p value <0.01). After chelation there is significant improvement of diastolic dysfunction and it has statistically significant correlation with the rate of decrease in ferritin (R^2=0.143 & p value <0.01).But there is no significant reduction in PASP with chelation therapy.

Conclusion: Cardiac diastolic dysfunction is a major manifestation of β thalassemia major patients. With successful chelation therapy the grade of diastolic dysfunction can be reverted. But in our study it is shown that the PAH once developed (mostly in E-β variants) cannot be reverted by oral chelation therapy.

KEYWORDS

Thalassemia Variants, Echocardiography, Diastolic Dysfunction

Introduction:

Iron overload is a problem in chronic haemolytic anaemia like β-thalassaemia major. Repeated blood transfusion, though improves quality of life, causes transfusion haemosiderosis. Iron is initially deposited in liver followed by iron deposition in endocrine glands and thereafter in heart.[*]

Life expectancy of patients with β-thalassaemia major is still limited by development of congestive heart failure as a result of cardiomyopathy[1] which is due to iron over-load.[2] Aggressive chelation therapy may prevent or delay the development of myocardial dysfunction or even may reverse it; but once overt heart failure has developed, only 50% of patients survive. The aim, therefore, is to begin treatment while the cardiomyopathy is still reversible[3]. However, early recognition of patients, at risk of heart failure, has been difficult, because global left ventricular function and exercise capacity in chronically transfused patients with iron overload may remain normal until late in the disease process.[4,5] Quantifying myocardial iron content has only recently become possible using magnetic resonance imaging (MRI) T2 cardiac software.[6,7] However, MRI is not widely available, time consuming and expensive. This limits the application of this technique especially in the developing countries where thalassaemia is most common. On the other hand, Echocardiography is more widely available. Hence we utilized Tissue Doppler Echocardiography for early detection of cardiac parameters in thalassaemia patients and measured iron overload by serum ferritin level. In patients with β-thalassaemia major a high incidence of cardiac involvement still exists despite improved prognosis with chelation therapy. We have compared the cardiac parameters after giving Deferasirox (DFX) monotherapy in one year period of follow up.

MATERIALS AND METHODS:

It was a cross sectional hospital based study, carried out in the Department of Paediatrics, Calcutta National Medical College & Hospital, Kolkata with the help of Department of Cardiology, Biochemistry & Pathology from June 2013 through May 2014. Institutional Ethics Committee of Calcutta National Medical College approved the study and written informed consent was obtained for each participant from one parent. Of all the patients with β-thalassemia and its variants, diagnosed by HPLC & having multiple transfusions without chelation, attending our thalassaemia unit, 100 patients belonging to age group of one to 12 years were selected for the study. Patients having major congenital anomaly and life-threatening conditions were excluded from the study.

Among all the patients taken into the study initially, 54 cases received regular chelation therapy subsequently. These 54 sample cases were considered as Group-1 and 2 before and after chelation respectively.

Detailed history was taken including total number of transfusions. Complete haemogram and chest x-ray were done. Serum iron, TIBC, serum ferritin were measured. LFT were done in all patients.

The cardiac profile of the patients was assessed by ECG, Echocardiography with color Doppler study and measurement of PASP (pulmonary arterial systolic pressure), TAPSE (tricuspid annular plane systolic excursion) and E / Em ratio.

PASP (pulmonary arterial systolic pressure) was measured from TR (Tricuspid Regurgitation) gradient by using the following formula.

PASP=4×TR^2+ right atrial pressure (RAP)
PASP > 35 mm of Hg was considered as PAH (pulmonary arterial hypertension).

MPAP(Mean Pulmonary arterial pressure)=0.61×PASP+1.95 mm Hg
RAP was measured as mentioned below:
RAP= 3 if IVC not dilated and compressible >50% with respiration.
= 8 if IVC dilated but compressible >50% with respiration
=15 if IVC dilated but compressible <50% with respiration

[Taken from **Guidelines for the Echocardiographic Assessment of the Right Heart in Adults: (J Am Soc Echocardiogr 2010)]**

Early ventricular filling velocity to early diastolic myocardial velocity ratio (E:Em) is an indicator of diastolic function of ventricular myocardium and it was captured by tissue doppler Echocardiography. E : Em ratio >15 was considered as abnormal indicating the presence of obvious diastolic dysfunction (DD).

TAPSE (tricuspid annular plane systolic excursion) is a measure of RV longitudinal function.

TAPSE < 16 mm indicates RV systolic dysfunction. It was measured from the tricuspid lateral
annulus.

[Taken from **Guidelines for the Echocardiographic Assessment of the Right Heart in
Adults: (J Am Soc Echocardiogr 2010)]**

All the informations were collected in predesigned standard proforma. Data obtained from the study were analyzed using SPSS version 17. We used regression analysis and from that we got linear, compound and logarithmic curves showing the relationship between the dependant and independent variables. We also used box plots to analyze the data.

RESULT AND ANALYSIS :

In our study, the E-β Thalassaemia constituted the major portion (about 72 %) of the samples under study. Majority of children (both male and female), under study, were affected by E-β Thalassemia. Out of total 67 male patients in our study, 45 (about 67 per cent) had E-β Thalassaemia. On the other hand, out of 33 total female patients in the study, 27 (about 82 per cent) had E-β Thalassaemia.

The frequency distribution of 100 samples according to their age and sex shows that maximum number of cases (both male & female) were within the age group of 6-9 years.

There is a positive correlation between the grade of diastolic dysfunction and the ferritn level in the pre chelation phase (R^2=0.33 & p value <0.01) (Table- 1).The mean value for ferritin remains highest (3978.61mg/dl) for Type-1(β major), and it is lowest (1025.50 mg/dl) for Type-3(S-β), (p value <0.01). The mean PASP value is higher (41.51mm of Hg) in E-β thalassaemia patients compared to the other thalassemia subgroups (p value <0.01) (Table- 2). There is also a positive correlation between the ferritin level and PASP among all patients in the pre chelation phase (R^2= 0.59 & p value< 0.05).

Table 1: Mean Ferritin levels in different grades of Diastolic Dysfunction (p value <0.05)

DD	Mean ferritin level	No of pts	Std. Deviation
.00	1546.3261	46	1185.60998
1.00	2637.5556	9	2361.42045
2.00	3087.4167	12	840.92411
3.00	3306.9667	30	1250.28120
4.00	5644.0000	3	39.94997
Total	2480.5900	100	1608.94131

Table 2: Mean PASP value in different types of thalassemia (p value is <0.05)

Type 1 = β-thal major Type 2 = Eβ-thal Type 3 = Sβ-thal.

Type	Mean PASP	N	Std. Deviation
1.00	34.1111	18	6.60560
2.00	41.5139	72	8.85882
3.00	31.2000	10	7.34544
Total	39.1500	100	9.15123

After chelation the Ferritin level significantly decreased as shown in Fig.-1 (Box plot) and there is significant improvement of diastolic dysfunction, and it has a statistically significant correlation with the rate of decrease in ferritin level (R2=0.143 & p value <0.01shown by the regression analysis) (Fig.2).

Fig 1 : Box plot showing decrease in ferritin level after chelation therapy (group 2) compared to Ferritin level before chelation (group 1)

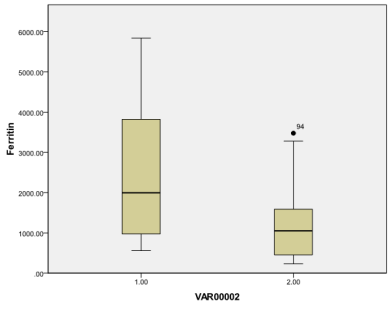
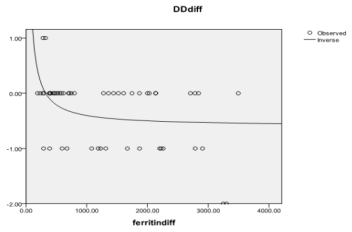


Fig 2: showing improvement of diastolic dysfunction (DD) after proper chelation therapy (Inverse correlation) (R^2=0.143 & p value <0.05)



Ddiff = – 0.596 + 192.8 (1/ FERRITINdiff) …… (ii) (R^2 = 0.143) (–4.844*) (2.941*)

Cross tabulation also shows an improvement in the grade of diastolic dysfunction (DD) in those 54 patients who had received chelation therapy regularly. Only 9% patients in group 2 had grade 3 DD compared to 90.9% in group 1 (before chelation) (Table 3). But there is no significant reduction in PASP with chelation therapy. The mean PASP value after chelation is 40.7 mm of Hg compared to 38.98 mm of Hg before chelation(Table 4a & Fig.- 3). Paired sample T test shows significant increment in PASP value after chelation (p value < 0.01) (Table- 4b).

VAR00002 * DD Cross tabulation(multiple response)

Table 3: VAR00002: 54 subjects who have undergone regular chelation therapy are grouped into grp1& 2(1: before chelation, 2; after chelation).The grade of DD has been compared between groups 1 & 2 and the improvement is assessed by the above cross tabulation.

		DD					Total
		.00	1.00	2.00	3.00	4.00	
1.00	Count	46	9	12	30	3	100
	% within DD	62.2%	64.3%	40.0%	90.9%	100.0%	64.9%
2.00	Count	28	5	18	3	0	54
	% within DD	37.8%	35.7%	60.0%	9.1%	.0%	35.1%
Total	Count	74	14	30	33	3	154
	% within DD	100.0%	100.0%	100.0%	100.0%	100.0%	100.0%

T test :

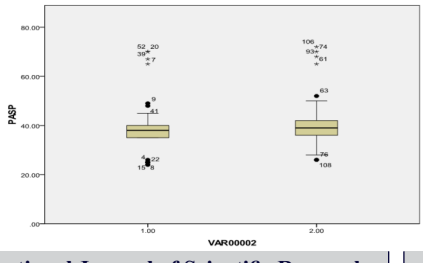
		Mean	N	Std. Deviation	Std. Error Mean
Pair 1	PASP	38.9815	54	10.16930	1.38387
	PASPc	40.7037	54	9.58109	1.30382

Paired Samples Test

Paired Samples Test									
		Paired Differences	t	df	Sig. (2-tailed)				
		Mean	Std. Deviation	Std. Error Mean	95% Confidence Interval of the Difference				
					Lower	Upper			
Pair 1	PASP - PASPc	-1.72222	2.20134	.29956	-2.32307	-1.12137	-5.749	53	.000

Table 4(a & b): PASP values before and after chelation(PASPc) (p value <0.05)

Fig 3: Box plot showing increase in mean PASP after chelation (group 2) with respect to before chelation (group 1) in 54 patients who received regular chelation therapy (VAR00002)



Discussion: In our study sample, the most prevalent type of thalassemia was E-β thalassaemia, next common being β-thalassaemia major and the least common was S-β thalassaemia.
Oliveri et. al. in their study observed that, Worldwide, patients with haemoglobin E-beta-thalassaemia (Hb Eβ-thalassaemia) represented approximately 50 per cent of those affected with beta thalassaemia[3]. The highest frequencies were observed in India, Bangladesh and throughout Southeast Asia, particularly in Thailand, Laos and Cambodia, where it is common for individuals to inherit alleles for both haemoglobin E (Hb E) and beta-thalassaemia[8].

According to the percentage distribution of all patients, females were more prevalent than males and most of the patients in the study population were in the age limit 3-9 yrs. The sex and age distribution may vary from study to study.

In the present study, in coherence with other studies, the prevalence of E-β patients was found to be highest[9]. And among them females are more prevalent.

Among the abnormal Echocardiographic findings, Pulmonary arterial hypertension (PAH) was most prevalent among E-β patients. It is consistent with the study of Aessopos A et al.[9]

Among the abnormal ECG findings, LVH and RVH were more prevalent in E-β patients. The RVH is due to pulmonary hypertension [10-11]. and LVH may be due to Volume overload. But due to lesser frequency of transfusion volume overload is more common in β major patients, so it may be concluded that in determining cardiac profile, Echocardiography is more sensitive than ECG.[12]

In this study, Echocardiographic evaluation of the thalassemia patients had shown a **positive correlation between Diastolic dysfunction (DD) and serum ferritin level.** Increase in iron overload causes increase in serum ferritin value as well as iron deposition in myocardium and thus grade of diastolic dysfunction increases. This is consistent with the study of Silvilairat et al.[13]

In this study, mean PASP (pulmonary arterial systolic pressure) was higher in type 2 (E-β) thalassemia patients in comparison to other types. Most of the E-β thalassaemia patients need lesser amount of transfusion compared to thalassemia major patients. But due to chronic hypoxia there is endothelial damage and development of early pulmonary hypertension. In a study by Aessopos. A et. al, it was shown that Pulmonary hypertension (PHT) was prevalent in patients with thalassemia intermedia (59.1%) and was thought to be the primary cause of congestive heart failure (CHF) in this patient population.[9]

Mean ferritin level was highest in β-thalassaemia major and lowest in S-β thalassemia, but the mean PASP was highest in E-β (type 2) patients. As β-thalassemia major patients are more dependent on blood transfusion, the iron overload is more in these patients reflecting a high ferritin level. On the other hand, in E-β thalassemia, endothelial dysfunction, as discussed earlier, results in high PASP value and early development of pulmonary hypertension.[9]

After treatment with DFX monotherapy there is significant reduction in serum ferritin level (Fig 1).This is well established in several studies [16-17]. The Mean PASP value remained more or less unchanged (Fig3 and table- 4a &b) even after chelation. There is improvement of diastolic function with chelation therapy. As the ferritin level decreases with chelation (ferritin difference increases) the grade of diastolic dysfunction improves (Inversely related)(Fig 2).There are not much studies comparing the change in pulmonary arterial pressure and cardiac diastolic function before and after chelation therapy in thalassemia patients as per medical literature. So our study is a bit unique.

Summary and Conclusion:
In the present study it has been found that among all the thalassemia patients, E-β comprises the major group in the population under study and this corroborates several other studies in this field.

Eβ-thalassaemia patients don't need frequent transfusions like β-thalassaemia major patients. But due to chronic anemia and hypoxia there is continuous ongoing endothelial damage resulting in Pulmonary arterial hypertension (PAH), denoted by Pulmonary arterial systolic pressure(PASP) > 35 mm of Hg. This observation is widely supported by other studies in this field. **But in our study it has been shown that the PAH once developed cannot be reverted by oral chelation therapy**.

In thalassemia β-major patients, frequent transfusions lead to severe iron overload and end organ damage. Cardiac diastolic dysfunction is a major manifestation of it. In this study it has been shown that there is a positive correlation between the grades of diastolic dysfunction and ferritin level (indicator of iron overload) and with successful chelation therapy the grade of diastolic dysfunction can be reverted.

Left ventricular ejection fraction (LVEF) is the reflector of left ventricular systolic function, and in this study it has been observed that LVEF is rarely influenced by iron overload. Though there is diastolic dysfunction due to restrictive pathology of myocardium, the systolic function is well preserved.

So, it can be concluded that cardiac dysfunction being a major manifestation in thalassemia patients due to chronic hypoxia, endothelial damage and iron deposition in tissues, early evaluation of cardiac status of these patients may reduce the morbidity and mortality resulted from the same. The ECG and Echocardiography are the most widely used modalities to evaluate cardiac status in developing countries like ours. .Echocardiography is more sensitive than ECG in this regard.

Echocardiography can detect diastolic dysfunction early and thus chelation therapy can be started in these patients to improve the outcome.

Conflict of interest: Nil

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Figure legends:
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groups 1 & 2 and the improvement is assessed by the above cross tabulation.

Table 4: PASP values before and after chelation (p value <0.05)
4a: T test
4b: Paired sample t test

Fig 1 : Box plot showing decrease in ferritin level after chelation therapy (group 2) compared to
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