A comparison of heart function and arrhythmia in clinically asymptomatic patients with beta thalassemia intermedia and beta thalassemia major

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ABSTRACT

Background: The goal of this study was to compare heart function and arrhythmia in clinically asymptomatic patients with beta thalassemia intermedia and beta thalassemia major.

Method: In this cross-sectional study, 60 patients with beta thalassemia major and 60 patients with beta thalassemia intermedia who had clinically no symptoms of arrhythmia and clinically normal heart function were evaluated using 24-hour ambulatory electrocardiogram monitoring and echocardiography. For data analysis SPSS ver.20 software was used. A P-value of less than 0.05 was considered statistically significant.

Results: The mean age of the beta thalassemia intermedia patients was 24.18 ± 7.9 years and the mean age in beta thalassemia major was 24.38 ± 7.7 years (P>0.05). Premature atrial contractions (PACs) were observed in 14 (23.3%) patients with beta thalassemia intermedia and in 22 (36.6%) beta thalassemi a major patients. Premature ventricular contractions (PVCs) were detected in 8 (13.3%) patients in the beta thalassemia intermediate group and 16 (26.6) patients in the beta thalassemia major group, respectively. The left ventricular diastolic dimension, end-diastolic volume, and stroke volume were significantly higher in beta thalassemia intermedia group (P<0.05). Pulmonary acceleration time as an indicator of pulmonary pressure was lower in beta thalassemia intermedia group.

Conclusion: Both atrial and ventricular arrhythmias were more common in the beta thalassemia major group. Higher end-diastolic volume and stroke volume were detected in the beta thalassemia intermedia group. Pulmonary acceleration time was lower in the beta thalassemia intermedia group, which can be an indicator of higher pulmonary pressure.

Introduction

Cardiac complications are a major problem for patients with beta thalassemia major and beta thalassemia intermedia. Impaired heart function, including heart failure and arrhythmias, is a common cause of death in these patients. These patients are also affected by cardiac dysfunction secondary to anemia. Blood transfusion partially overcomes these problems, but patients will resultantly face complications from the deposition and accumulation of iron in their heart [1–4].

Cardiomegaly and left ventricular dysfunction in untreated children can lead to advanced-stage heart failure [5,6]. In non-transfusion-dependent thalassemia patients, like thalassemia intermedia, iron overload will also occur due to an increased iron absorption.

The aim of this study was to compare heart function and arrhythmia in clinically asymptomatic patients with beta thalassemia intermedia and beta thalassemia major.

Materials and methods

This cross-sectional study was conducted in the thalassemia clinic of Shiraz University of Medical Sciences, Shiraz, Iran from June 2014 to May 2015.

A sample size of 60 patients for each group of beta thalassemia major and beta thalassemia intermedia was calculated to achieve an α=0.05 and an accuracy of 12.4.

All included patients with beta thalassemia major and beta thalassemia intermedia were over 5 years-old, without any congenital heart disease, and with clinically normal heart function classification (NYHA Class 1). Diagnosis of thalassemia major and intermedia was based on clinical findings, complete blood count, and hemoglobin electrophoresis. Fasting blood ferritin was measured by Mini Vidas method (Vidas Machine-France). The mean hemoglobin during the previous 6 months was collected from the patients’ charts. Beta thalassemia intermedia patients were non-transfusion dependent and had been treated with hydroxyurea, folic acid, and iron chelation if serum ferritin was above 500 ng/dL.
Patients with β-thalassemia major had regular blood transfusions at intervals of 2–4 weeks. All of the β-thalassemia major patients received iron chelation therapy. The patients were selected randomly from patients who were registered at the Hematology Research Center Outpatient Thalassemia Clinic of Shiraz University of Medical Sciences, in Shiraz, Iran. This study was approved by the Ethics Committee of Shiraz University of Medical Sciences. Written consent was taken from patients or their legal guardians before the start of the study. Patients were examined by an expert hematologist and cardiologist. Twenty-four hour ambulatory ECG monitoring was performed by Holter set (Braemar Inc., America). Echocardiography was performed by Mindray DC 7 (Shanghai, China) echocardiography machine using a 3 MHz probe.

All M-mode, two-dimensional, Doppler, and pulse tissue Doppler echocardiographic measures were performed by one cardiologist in left lateral decubitus position. Ejection fraction, shortening fraction, and septal and posterior wall thickness in systole and diastole were measured in the left parasternal long-axis view. The pulsed Doppler sample volume was placed at the mitral valve and tricuspid tips, and three cardiac cycles were recorded from the apical window. Early (E) and late wave (A) peak velocities (m/s) and their ratios were determined for evaluation of diastolic function. Pulmonary acceleration time was measured in the parasternal short-axis view.

Pulsed tissue Doppler tissue imaging was obtained with the sample volume placed at the lateral corner of the mitral annulus, subsequently on the medial (or septal) and tricuspid corner in the apical four chamber view, and then at the anterior and posterior wall in the parasternal short-axis view. In each region, systolic (S), early (Ea), and late (Aa) diastolic velocities were recorded.

SPSS for windows version 20 (SPSS Inc, Chicago) was used for statistical analysis. The numeric data are presented as mean ± standard deviation. The t-test was used to compare quantitative data between patients and controls. Chi square test was used to compare sex ratio between the two groups. Pearson correlation was used to evaluate correlations between echocardiographic parameters and hematologic parameters. A P<0.05 was considered significant for all the statistical tests.

Results

In this study, 60 patients with β-thalassemia major and 60 patients with β-thalassemia intermedia were enrolled in the study. The mean age in the thalassemia major group was 24.38 ± 7.7 years and 23.97 ± 8.1 years (P>0.05) in the thalassemia intermedia group. Demographic and hematologic parameters are shown in Table 1.

24-hour ambulatory monitoring

Premature atrial contractions (PACs) were observed in 14 (23.3%) patients with beta thalassemia intermedia and in 22 (36.6%) beta thalassemia major patients. Premature ventricular contractions (PVCs) were detected in 8 (13.3%) patients in the thalassemia intermedia group and 16 (26.6%) patients in the thalassemia major group, respectively. Other types of arrhythmias were reported in two patients with thalassemia major (atrial fibrillation in one subject, and supraventricular tachycardia in one subject).

M-mode echocardiography

The left ventricular diastolic diameter in diastole, end-diastolic volume, shortening fraction, and stroke volume were significantly higher in patients with beta thalassemia intermedia (P>0.05, Table 2).

Doppler echocardiography

Doppler echocardiography of mitral and tricuspid valve peak velocity showed that the early diastolic (ET, Em)

Table 1. Demographic and hematologic parameters in patients with thalassemia major and intermedia.

| Variable      | Thalassemia intermediate N=60 | Thalassemia major N=60 | P-value |
|---------------|-------------------------------|------------------------|---------|
| Sex (male)    | 28                            | 30                     | 0.775   |
| Age (years)   | 23.97±8.1                     | 24.38±7.7              | 0.188   |
| Weight (Kg)   | 41.87±3.9                     | 41.35±4.8              | 0.270   |
| Hemoglobin    | 9.09±1.12                     | 9.47±0.84              | 0.040   |
| Ferritin (ng/dl) | 1724.43±1664.2                | 1035.78±2039.9         | 0.046   |

Table 2. Parameters obtained by M-Mode echocardiography in patients with thalassemia major and intermediate.

| Variable      | Thalassemia intermediate N=60 | Thalassemia major N=60 | P-value |
|---------------|-------------------------------|------------------------|---------|
| IVSD-d (cm)   | 1.00±0.2                      | 1.01±0.2               | 0.822   |
| LVID-d (cm)   | 5.06±0.62                     | 4.80±0.6               | 0.026   |
| LVPWD-d (cm)  | 9.95±0.2                      | 9.69±0.1               | 0.680   |
| IVSD-s (cm)   | 1.29±0.2                      | 1.21±0.2               | 0.076   |
| LVID-s (cm)   | 2.89±0.5                      | 2.91±0.5               | 0.822   |
| LVPWD-s (cm)  | 1.13±0.2                      | 1.07±0.2               | 0.177   |
| EDV (cm)      | 124.62±34.4                   | 110.38±34.1            | 0.025   |
| ESV (cm)      | 33.58±14.0                    | 34.66±16.3             | 0.751   |
| EF (%)        | 72.96±8.8                     | 69.94±8.2              | 0.055   |
| FS (%)        | 42.65±8.5                     | 39.7±7.3               | 0.048   |
| SV (ml)       | 91.26±30.5                    | 76.13±20.4             | 0.005   |

IVSD-d, interventricular septum diameter in diastole;LVID-d, left ventricular internal diameter in diastole; LVPWD-d, left ventricular posterior wall diameter in diastole; IVSD-s, interventricular septum diameter in systole; LVID-s, left ventricular internal diameter in systole; LVPWD-s, left ventricular posterior wall diameter in systole; EDV, end-diastolic volume; ESV, end systolic volume; EF, ejection fraction; FS, fractional Shortening; SV, stroke volume.
and late diastolic (AT, Am) velocities had no significant difference. Pulmonary acceleration time was significantly lower in beta thalassemia intermedia patients ($P=0.028$, Table 3).

**Pulse tissue Doppler echocardiography**

Systolic velocity of the septum and lateral tricuspid annulus, and early diastolic velocity of mitral valve were significantly higher in thalassemia intermedia group ($P<0.05$, Table 4).

Ferritin level had a statistically significant correlation with IVSS ($P=0.047$, $r=0.25$), SM ($P=0.003$, $r=−0.37$), AaM ($P=0.027$, $r=−0.28$), ST ($P=0.017$, $r=−0.31$), and SS ($P<0.001$, $r=−0.45$) in beta thalassemia intermedia patients. Hb level had a correlation with IVSD ($P=0.036$, $r=−0.27$) in the beta thalassemia intermedia group. In the beta thalassemia intermedia patients with splenectomy, ST was less than in patients without splenectomy (15.32±0.37 vs 17.11±3.31, $P=0.027$).

In beta thalassemia major patients, there was no statistically significant correlation between ferritin and echocardiography findings. In beta thalassemia major patients who had splenectomy, E wave of tricuspid (78.55±16.47 vs 87.44±15.1, $P=0.034$) was significantly lower.

**Discussion**

Other studies have shown that heart failure and diabetes are the most common causes of hospital admission in patients with thalassemia [7,8]. Early detection of arrhythmias and cardiovascular disorders in patients with thalassemia is a major issue that has recently gained a great deal of attention. This issue is very important because these patients are clinically asymptomatic and an effort to find a suitable method for early diagnosis of these disorders is necessary.

In this study, 46 (38.33%) patients had arrhythmia in the 24-hour ambulatory monitoring (Holter). In a study by Qureshi et al. [9] on transfusion-dependent beta thalassemia patients, 37% had arrhythmia. In our study, atrial fibrillation and supraventricular tachycardia were reported in two patients with beta thalassemia major. In a study by Koonrungsesomboon et al. [10], in addition to these arrhythmias, heart block, ventricular tachycardia, and atrial flutter were also reported.

In our study both PACs and PVCs were more common in beta thalassemia major patients. Although PACs seem to be a benign rhythm disturbance, the existence and frequency of PACs is usually dependent upon the presence of structural heart disease. PACs are particularly frequent in patients with left ventricular dysfunction regardless of etiology. Most individuals with PACs are asymptomatic but PACs may lead to palpitations or the sensation of drop beats. In a study that followed 402 men without myocardial infarction or stroke for 14 years, a high frequency of PACs without atrial fibrillation was associated with an increased risk of stroke [11]. No therapy is required for PACs in the asymptomatic subjects. For patients with symptomatic PACs, symptoms may be decreased by discontinuing potential precipitating habits such as smoking, coffee intake, alcohol intake, and stress. Treatment with beta blocker can reduce the symptoms related to PACs.

In our study PVCs were less frequent than PACs in both groups. PVCs usually produce no symptoms in the majority of patients. PVCs rarely cause hemodynamic compromise except in patients with frequent ectopy and depressed left ventricular function. Occasionally, frequent PVCs can result in left ventricular dysfunction, which improves following suppression of the PVCs or ablation [12,13]. There is no evidence that the suppression of PVCs can extend life expectancy or reduce the risk of cardiac events in patients with or without heart disease. Although PVCs are often thought to be of clinical significance, particularly in patients with normal heart function, most studies showed an increased mortality in patients with PVCs [14]. More studies are required to evaluate the significance of PACs and PVCs in patients with beta thalassemia. Hemoglobin levels in patients in both groups

| Variable | Thalassemia intermediate | Thalassemia major | $P$-value |
|----------|--------------------------|-------------------|-----------|
| Em (cm/s) | 119.25±22.7 | 111.94±18.2 | 0.058 |
| Am (cm/s) | 77.45±25.7 | 79.72±20.6 | 0.123 |
| ET (cm/s) | 83.00±16.2 | 76.25±16.6 | 0.027 |
| AT (cm/s) | 58.27±17.4 | 58.44±17.1 | 0.999 |
| PAT(m/s) | 123.75±23.8 | 132.87±19.1 | 0.028 |

Em, early diastolic velocity of mitral valve; Am, late diastolic velocity mitral valve; ET, early diastolic velocity of tricuspid valve; AT, late diastolic velocity of tricuspid valve; PAT, pulmonary acceleration time.
were not significantly correlated with the prevalence of arrhythmia in our patients. Both groups had higher serum ferritin levels in subjects with arrhythmias, but this difference was not statistically significant.

The left ventricular diastolic dimension, end-diastolic volume, and stroke volume were significantly higher in the beta thalassemia intermedia group ($P<0.05$). This increase might be due to lower hemoglobin level in patients with beta thalassemia intermedia. In our study there was no significant difference in the left ventricular wall between the two groups. However, in a study by Noori et al. [15], left ventricular wall thickness was significantly higher in the beta thalassemia major group. This difference might be due to the selection of younger patients with mean age of 16 years in their study. In our previous study of patients with beta thalassemia intermedia, there was no difference in wall thickness with that of normal subjects [16]. In our study, fractional shortening in the beta thalassemia intermedia group was more than that of the beta thalassemia major group, a finding that is compatible with the results of Noori’s study [15]. In a study by Aessopos et al. [17], cardiac dimensions, left ventricular shortening, ejection fractions, and cardiac output were significantly higher in patients with thalassemia intermedia.

Doppler study of diastolic velocities showed no statistically significant difference between patients with thalassemia major and intermedia. To evaluate pulmonary arterial hypertension (PAH), pulmonary acceleration time was used in this study. In patients with thalassemia intermedia, PAT was significantly less than in patients with thalassemia major which is an indicator of higher pulmonary artery pressure in subjects with thalassemia intermedia. In our previous study, 37 patients with beta thalassemia intermedia were compared to the control group, which had a 21% prevalence of pulmonary hypertension in patients with beta thalassemia intermedia. Evaluation of risk factors for pulmonary hypertension in patients with beta thalassemia intermedia. Evaluation of risk factors for pulmonary hypertension in patients with beta thalassemia showed that the female sex and low hemoglobin levels were risk factors for these conditions [15]. In our current study, we found that PAH is significantly associated with hemoglobin level.

Comparison of tissue Doppler in thalassemia major and thalassemia intermedia patients in our study showed that systolic motion of lateral tricuspid and septum was significantly increased in thalassemia intermedia.

There are a few studies for evaluation of complications in thalassemia major and intermedia. In the study by Noori et al., echocardiographic findings in a group of thalassemia intermediate patients with no signs of cardiac involvement by physical examination, chest x-ray, and electrography were compared with healthy individuals. The results of Noori’s study showed that patients with thalassemia intermedia were more likely than healthy people to develop heart dysfunction [11].

In a study by Yaman et al., complication rates were significantly higher among thalassemia major patients compared to thalassemia intermedia patients. Cardiac complications developed in 22.4% of their patients [18].

In this study, ferritin levels had correlation with heart wall diameter in patients with thalassemia intermedia ($P<0.05$) and systolic motion of mitral and septum. The findings of our study are compatible with the results of Ozdogan and colleagues [18]. However, the Yaman et al. [19] study showed no statistically significant relationship between complications and mean ferritin levels. However, more studies are needed to determine the significance of these correlations.

There was significant correlation between hemoglobin level and septal thickness in beta thalassemia intermedia. Similar correlation was not detected in the beta thalassemia major group which could be due to transfusion and chelation therapy.

Some studies evaluated the accuracy of echocardiography in comparison to cardiac magnetic resonance imaging, which showed that when cardiac magnetic resonance imaging is not available, echocardiography has a significant role in management of patients with thalassemia major [20,21].

**Limitations of the study**

Estimation of pulmonary artery pressure by pulmonary acceleration time is evaluated in some studies but the gold standard for detection of pulmonary artery pressure is angiography which was not used in this study. Cardiac magnetic resonance imaging is noninvasive and is reliable in assessing the anatomy and function of the heart. The T2* method is also a noninvasive method for detection of iron load which was not used in this study due to limitations in accessibility.

**Conclusion**

According to the results of this study both atrial and ventricular arrhythmias were more common in beta thalassemia major than in patients with beta thalassemia intermedia. PAT was lower in beta thalassemia intermedia which might be an indicator of higher pulmonary pressure. Consequently, serial echocardiography and Holter monitoring are suggested in asymptomatic patients with beta thalassemia major and intermedia for the early diagnosis of heart dysfunction, pulmonary hypertension, and arrhythmias and for appropriate treatment.

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Disclaimer statements

Contributors H. Amoozgar contributed to drafting and editing the manuscript. S. Zeighami wrote the manuscript and performed the data collection. S. Haghpanah done statistical analysis. M. Karimi contributed to the study design, concept, and editing the manuscript.

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Conflicts of interest None declared

Ethics approval This study was approved by the Ethics Committee of Shiraz University of Medical Sciences.

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