



# Efficacy of High Dose and Short Course of Deferoxamine Infusion on Cardiac Remodeling Of Children with Thalassemia Major

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## Abstract

**Background:** Speckle tracking echocardiography has great value in evaluation of regional and global myocardial function.

**Objectives:** The goal of this study was an assessment of cardiac function and remodeling in children with thalassemia major after infusion of a high dose of deferoxamine during a short course by speckle echocardiography and evaluate the efficacy of this imaging modalities in the early recognition of recovering of myocardial dysfunction.

**Methods:** In a prospective study between Feb 2014 till 2017 conventional 2 dimensional and speckle tracking echocardiography were done consecutively on 21 patients with beta-thalassemia major before intravenous infusion of high dose of deferoxamine (50 mg/kg) for 5 days and then after 3 months echocardiographic measurements repeated for assessment of efficacy of deferoxamine infusion on ventricular function and cardiac remodeling of our study population.

**Results:** Serum ferritin of all patients reduced significantly ( $P < 0.001$ ). Ejection fraction was improved after the therapy ( $P < 0.001$ ). Mitral E/A velocity ratio after therapy increased significantly ( $P < 0.001$ ). Strain imaging measures showed an increase in apical lateral, mid-lateral, basal lateral, mid-septal, basal septal left ventricular longitudinal wall strain three months after the use of high dose deferoxamine ( $P < 0.001$ ). Apico-septal wall strain measurements of the left ventricle did not change significantly after high dose deferoxamine ( $P = 0.144$ ).

**Conclusions:** Intravenous infusion of high dose of deferoxamine after chelating of iron results in reduction of serum ferritin which may cause washout of cardiac deposit of iron with consequent improvement of cardiac function and remodeling.

**Keywords:** Beta Thalassemia Major, Strain Imaging, Deferoxamine, Myocardial Function

## 1. Background

Beta thalassemia major (TM) results in severe anemia mainly due to extravascular hemolysis and ineffective erythropoiesis (1, 2). Long-term survival of patients depends on regular packed red cell transfusion which ultimately causes iron overloading of various major organs containing the myocardium. Because myocardial dysfunction and heart failure is the main reason of death, regular use of oral or subcutaneous injection of a chelating agent such as deferoxamine by infusion pump will reduce iron overloading in different organs (3-7).

Mortality of patients with intractable heart failure is as high as 50%, hence early detection of cardiac involvement and proper treatment may improve wellbeing and survival of patients (3-5, 8).

Several studies have revealed that intravenous infusion of high dose of deferoxamine during a short course may reverse myocardial dysfunction and improve symptoms of congestive heart failure (CHF) (1, 2). Nowadays speckle tracking echocardiography as a new and sensitive modality is used for early detection of segmental and global myocardial dysfunction in different types of heart diseases (8, 9).

## 2. Objectives

This study was designed to clarify the effect of high dose and a short course of intravenous deferoxamine on segmental and global cardiac function and remodeling by speckle tracking echocardiography in children with TM and evaluate the efficacy of this imaging modality in the

early recognition of recovering of myocardial dysfunction in comparison to conventional echocardiography.

### 3. Methods

#### 3.1. Study Population

Between Feb 2014 - Feb 2017 twenty-one of known patients with TM who were candidates for high dose intravenous infusion of deferoxamine were included in this study. Paraclinical work up including hemoglobin level and serum ferritin level were measured before and 3 months after intravenous deferoxamine therapy. All patients were on regular packed red blood cell transfusion. None of the study population had overt heart failure and not receiving any cardiovascular medication. Deferoxamine with a dosage of 50 mg/kg/day for 5 days was infused via intravenous route under the supervision of both hematologist and cardiologist for any complication related to the procedure.

Inclusion criteria for the study were: The patient with beta-thalassemia major on regular blood transfusion, no sign of heart failure, arrhythmia, serum ferritin above 500 ng/mL, and cardiac iron overloading that was detected by T2\* MRI results score less than 20 ms.

#### 3.2. Echocardiography

Echocardiography studies were performed with a MyLab gold 30 echocardiography machine (MyLab 30, Esaote Gold S.P.A, Italy) using 2 - 4 MHz probe. One pediatric cardiologist measured all echocardiographic quantities, and several parameters of two dimensional, Doppler, pulse tissue Doppler and longitudinal strain function of the left ventricle were considered to improve reliability.

M-mode echocardiography contained interventricular septum diameter, left ventricular posterior wall diameter, and ejection fraction (EF) in parasternal long-axis assessment. Peak early diastolic velocity (E), peak velocity during atrial contraction (A), and their ratio were measured with pulse Doppler at the level of mitral and tricuspid leaflets.

For gaining the tissue Doppler, sample volume was set on 5 millimeters and placed at the septal side of mitral annulus and then on lateral side of mitral annulus. In each site peak systolic velocity of myocardium (S), peak early diastolic velocity of myocardium (E') and peak late diastolic (A') velocity of myocardium were recorded. A cine loop of three sequential beats was recorded and mean value of three measured velocities obtained for statistical analysis.

#### 3.3. Strain Imaging Measures

For strain imaging a sector scan angle of less than 60° was selected. Three cardiac cycles with electrocardiographic monitoring were acquired in each region and stored for future examination. Tracking was performed automatically by software and when necessary, it was adjusted manually by a pediatric cardiologist to detect the whole endocardium.

Evaluation of the longitudinal strain and strain rate was performed with X Strain software as an offline measurement. The software automatically divided the cross-sectional of four-chamber view of the obtained myocardial strain into six divisions. Left ventricular sections that were recorded to be analyzed were the basal segment septum, mid-segment of septum and apical segments of the septum, and basal segment, mid-segment of lateral wall and apical segments of the lateral wall of left ventricle in a standard four-chamber view. The global left ventricular longitudinal strain was calculated by the software.

#### 3.4. Statistical Analysis

Statistical studies were done with SPSS for windows version 22 (SPSS Inc., Chicago). The variables were defined through the values, means, and standard deviations (SD). For comparing between each patient before and 3 months after receiving high dose deferoxamine, paired *t*-test was used. P less than 0.05 was statistically significant in this study.

### 4. Results

Our study included 21 children with TM (11 females and 10 males) who were  $15.74 \pm 1.79$  years old. All of the patients had ferritin level above 500  $\mu\text{g/L}$  in their blood sample and sixteen patients had serum ferritin level above 2000  $\mu\text{g/L}$ , three of whom had serum ferritin level above 10000  $\mu\text{g/L}$  before using high dose injection of deferoxamine. The patients' characteristics including age, sex, magnetic resonance imaging results, and serum ferritin before and after high dose deferoxamine are shown in [Table 1](#).

Three months after injection of high dose deferoxamine, serum ferritin level of all the patients reduced significantly ( $P < 0.001$ ). Serum ferritin level of two patients reached below 500  $\mu\text{g/L}$  and that of thirteen patients was above 2000  $\mu\text{g/L}$ ; none of them had serum ferritin above 10000  $\mu\text{g/L}$ . Two patients with serum ferritin below 1000  $\mu\text{g/L}$  that were included in the study had supraventricular tachyarrhythmia in the surface electrocardiography before starting deferoxamine which improved after three months.

**Table 1.** Patients' Characteristics Including, Sex, Age, Cardiac Iron Overloading by MRI T2\*, Serum Ferritin Before and After High Dose Deferoxamine<sup>a</sup>

Patient	Sex	Age, y	MRI T2*, ms	Serum Ferritin Before Therapy, Mic/L	Serum Ferritin After Therapy, Mic/L
1	F	17	8	15600	9500
2	M	18	11	4600	2000
3	M	15	8	7000	3000
4	M	13	8	6000	2900
5	F	16	16	2200	1000
6	F	17	9	7700	4000
7	F	17.5	10	5000	3000
8	M	18	7	9000	7000
9	F	16.6	8	6000	3000
10	F	15	10	6000	4000
11	M	14	7	6000	5500
12	F	13	9	6000	4200
13	M	12	16	4500	2000
14	M	17	15	1600	1000
15	F	13.5	16	1200	700
16	M	16	7	8000	5000
17	F	17	14	1000	700
18	M	17.8	6	10000	6000
19	M	16.6	7	10000	8000
20	F	15.7	19	580	420
21	F	15	18	850	500

<sup>a</sup>P = 0.001 for serum ferritin before and after therapy.

#### 4.1. M-Mode and Doppler Parameters

EF increased from  $63.81 \pm 7.34$  before therapy to  $64.62 \pm 6.90$  after the use of high dose IV deferoxamine ( $P < 0.001$ ). Two patients with EF below 50% before receiving high dose deferoxamine, showed an increase in EF after treatment. Transmitral E/A ratio increased from  $1.66 \pm 0.38$  to  $1.74 \pm 0.36$  after using high dose deferoxamine ( $P < 0.001$ ).

#### 4.2. Tissue Doppler Imaging Echocardiography

The TDI measures revealed significant alterations of the left ventricular function after receiving high dose deferoxamine ( $P < 0.001$ , Table 2).

#### 4.3. Strain Imaging Measures

Strain values of all cardiac segments except apical septal increased significantly after using high dose IV deferoxamine ( $P < 0.001$ ). Strain measures of the apical lateral left ventricular (LV) wall, mid-lateral LV wall, and mid-septal LV wall was significantly increased in patients after using high dose deferoxamine ( $P < 0.001$ ), but the apical septal

left ventricular wall did not change significantly ( $P = 0.144$ , Table 3).

Table 4 shows the results of strain rate values in each segment of the left ventricle.

## 5. Discussion

It has been documented that a short course of treatment with intravenous infusion of deferoxamine has short-term benefits in patients with  $\beta$  thalassemia (10, 11), so we designed to evaluate remodeling and myocardial function of children with  $\beta$  thalassemia patients for the efficacy of high dose intravenous deferoxamine by speckle tracking echocardiography.

In the present study, EF had a small increase in normal range but this small increase was statistically significant after using high dose deferoxamine. In a study by Bernard et al. by using 24-hour deferoxamine, intravenous infusion for high-risk beta-thalassemia patients, serum ferritin reduced significantly and EF improved significantly after

**Table 2.** Tissue Doppler Imaging (TDI) Measurements Before and After High Dose Deferoxamine Using Mean  $\pm$  SD

	Before Deferoxamine, m/s	After Deferoxamine, m/s	P Value
SM	0.081 $\pm$ 0.018	0.092 $\pm$ 0.017	< 0.001
E'M	0.101 $\pm$ 4.15	0.134 $\pm$ 0.038	< 0.001
A'M	0.071 $\pm$ 0.026	0.074 $\pm$ 0.023	< 0.001
SS	0.073 $\pm$ 0.016	0.075 $\pm$ 0.014	< 0.001
E'S	0.102 $\pm$ 0.035	0.115 $\pm$ 0.029	< 0.001
A'S	0.081 $\pm$ 0.025	0.085 $\pm$ 0.021	< 0.001

Abbreviations: A'M, lateral mitral annulus late diastolic velocity; A'S, septal mitral annulus late diastolic velocity; E'M, lateral mitral annulus early diastolic velocity; E'S, septal mitral annulus early diastolic velocity; SM, lateral mitral annulus systolic velocity; SS, septal mitral annulus systolic velocity.

**Table 3.** Strain Measurements Results of Different Segments of the Left Ventricle Using Mean  $\pm$  SD and P Values Before and After High Dose Deferoxamine

Strain Measurements/LV Segments	Before Deferoxamine, cm/s	After Deferoxamine, cm/s	P Value
Apical lateral wall	-12.36 $\pm$ 4.84	-18.53 $\pm$ 7.24	< 0.001
Mid-lateral wall	-12.56 $\pm$ 4.07	-19.50 $\pm$ 4.82	< 0.001
Mid-septal wall	-13.85 $\pm$ 5.74	-21.53 $\pm$ 5.93	< 0.001
Apical septal wall	-12.58 $\pm$ 5.43	-13.42 $\pm$ 6.05	0.144
Basal lateral wall	-13 $\pm$ 5.07	-19.53 $\pm$ 5.94	< 0.001
Basal septal wall	-14.75 $\pm$ 6.30	-21.14 $\pm$ 6.66	< 0.001

**Table 4.** Strain Rate Measurements Results of Different Segments of the Left Ventricle (Using Mean  $\pm$  SD and P Values); Before and After High Dose Deferoxamine

Strain Rate Measurements/ LV Segments	Before Deferoxamine, cm/s	After Deferoxamine, cm/s	P Value
Apical lateral wall	-0.68 $\pm$ 0.28	-1.17 $\pm$ 0.30	< 0.001
Mid-lateral wall	-0.83 $\pm$ 0.25	-1.24 $\pm$ 0.26	< 0.001
Mid-septal wall	-0.84 $\pm$ 0.27	-1.28 $\pm$ 0.32	< 0.001
Apical septal wall	-1.01 $\pm$ 0.46	-1.07 $\pm$ 0.43	0.144
Basal lateral wall	-0.99 $\pm$ 0.30	-1.43 $\pm$ 0.31	< 0.001
Basal septal wall	-1 $\pm$ 0.37	-1.43 $\pm$ 0.35	< 0.001

medication (12). In another study by Rashidi et al. beta-thalassemia patients with heart failure were selected and high dose deferoxamine was used, showing significant improvement of EF (13). In our study, however, none of the patients showed clinically signs and symptoms of heart failure but, as previously mentioned, EF improved significantly after three months.

Also, transmitral diastolic E/A ratios increased significantly after therapy. This was probably due to the accelerated left ventricular relaxation after reducing serum ferritin and a decrease in iron overloading.

Serum ferritin levels in patients reduced significantly after using high dose deferoxamine. In a study by Rashidi et al. it was found that high dose deferoxamine can reduce serum ferritin in short time; our study showed a decrease of serum ferritin in a short time after administration (13).

The advantage of tissue Doppler and speckle echocar-

diography in recognition of subclinical myocardial dysfunction has also been confirmed in other diseases (14).

In a study, Hamdy compared the results of tissue Doppler and strain echocardiography in improvement of ventricular function in beta thalassemia patients after chelating therapy. They showed that strain imaging modality can detect early changes in myocardial function when compared with tissue Doppler. In addition, it was shown that high dose chelating therapy could improve myocardial systolic function by strain echocardiography (15). In our study, strain measures of the left ventricular basal and lateral wall improved significantly after high dose deferoxamine after three months, but apical septal left ventricular septum strain measurements did not change significantly. However, we suggest more follow up time and more patients should be studied to see the changes of strain patterns of different components of the left ventri-

cle after high dose of chelating therapy.

In a study by Bay et al. conventional and strain rate imaging echocardiography were compared in asymptomatic children with beta-thalassemia major and concluded that left ventricle mass and volume indexes might be more sensitive during childhood (10). Other modalities like cardiac magnetic resonance imaging can evaluate the myocardial ventricular dysfunction in these patients; however, high expenses, reduced availability, and more time needed to do magnetic resonance imaging are the limitations of this modality, so based on this study we suggest the use of strain imaging echocardiography as a sensitive and more available non-invasive tool for evaluation of myocardial systolic function in patients with beta-thalassemia major.

### 5.1. Limitation of Study

The small number of patients and short time of follow up were the main limitations of our study.

We suggest higher number of studied population and longer duration of follow up in upcoming studies.

### 5.2. Conclusions

The current study points to significant changes in the LV ejection fraction and serum ferritin and also strain imaging measures on the epicardium and endocardial surfaces of basal and lateral left ventricular wall. After high dose deferoxamine therapy, rapid changes and improvement of the LV systolic function can take place in the basal and lateral left ventricular wall but the apical septum of the left ventricle could not show this improvement in a short time period of follow up. High dose IV deferoxamine therapy can be considered in selective patients with  $\beta$  TM with iron overloaded hearts and speckled tracking echocardiography can be used as a modality for evaluation of myocardial function in such patients during and also after treatment with high dose chelating therapy.

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### Footnotes

**Authors' Contribution:** Mehdi Shahryari: collecting data, preparing of the manuscript, and final revision; Nima Mehdizadegan: collecting data, preparing of the

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**Patient Consent:** For echocardiography after explaining the study objectives informed consent was obtained from each patients or their parents/guardian. In accordance with the local ethical standards of Shiraz University of Medical Sciences Research Committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards, all procedures were performed.

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