Evaluation of Cardiac Complications in Patients with Thalassemia Major Using Serum Ferritin Levels

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Abstract

Introduction: Heart failure followed by myocardial iron overload is the most common cause of death in patients with thalassemia major undergoing regular blood transfusions. Although treatment with deferoxamine has greatly reduced the risk of heart failure, many thalassemia major patients still die of heart failure. Serum ferritin level is the best indicator to assess iron overload periodically in these patients. The present study aimed to evaluate cardiac complications in patients with thalassemia major using serum ferritin level.

Methods: This was a descriptive, cross-sectional study on 130 patients with thalassemia major in Cooley's Center in Motahari Hospital. Serum ferritin was measured for 3 months and compared with echocardiographic findings. Collected data was analyzed using SPSS 17, t-test and ANOVA.

Findings: Of 130 patients with thalassemia major in this center, 48.22% were males and 51.78% were females. Of total patients, serum ferritin level was less than 1000 ng/ml in 28 patients (21.54%) and greater than 1000 ng/ml in 102 patients (78.46%). Two patients suffered from impaired left ventricular contractility and one patient suffered from left ventricular dilatation in those patients that serum ferritin level was greater than 1000 ng/ml. Meanwhile, 11.64% of patients experienced pulmonary hypertension. Echocardiographic findings showed evidence of pericardial effusion (0.98%). In addition, 64.60% developed tricuspid insufficiency and 60.71% developed mitral insufficiency.

Conclusion: According to the above mentioned materials, 2.30% of patients developed multiple degrees of heart failure. Mean serum ferritin level was 3740 ng/ml. It seems that monitoring serum ferritin level control is an important step to prevent heart failure because serum ferritin level was greater than 1000 ng/ml in patients with heart failure in this study.

Key words: Thalassemia major, Serum ferritin level, Deferoxamine, Heart failure

INTRODUCTION

Thalassemia is a heritable blood disorder. One hundred thousand children are born with this disease in the world annually. All types of thalassemia are inheritable and passed from parents with carriers of thalassemia recessive gene. Most of these patients seem healthy at the first sight (1). Different methods are used to diagnose the disease but most of these methods are based on genetic studies and blood tests. Iran is located on thalassemia belt. There are 20000 patients with thalassemia in Iran according to statistics. Daily, 40 new cases of thalassemia are added to patients with heart disease (1500 new cases in an annual rate). A new thalassemia case is born every 6 hours in Iran according to statistics. Thalassemia demands great capital in any country for treatment [2]. This disease is caused by mutations in globin genes, which either reduces or stops synthesis of one or multiple globin chains. In fact, impaired synthesis of globin chains leads to accumulation of additional chains that ultimately impairs development of red blood cells [3]. Thalassemia refers to impaired synthesis of one or multiple globin chains. This causes an imbalance in synthesis of globin chains, which damages cellular tissues.
and impairs function of globin precursors [4]. Thalassemia is classified into different categories based on clinical symptoms and accumulation of additional globin chains in red blood cells (alpha chain in beta-thalassemia and beta chain in alpha-thalassemia). However, accumulation of either alpha or beta chain changes characteristics of red blood cell membrane. These changes lead to ineffective hematopoiesis and peripheral hemolysis in a large group of thalassemia patients [5]. Synthesis of either alpha or beta chain determines alpha chain-to-beta chain ratio, which is a certain constant figure in every organism. Any change in this ratio and excess synthesis of one chain over the other leads to development of different types of thalassemia and eventually damages red blood cells [6]. In homozygous form of beta-thalassemia, reduced synthesis of beta chain leads to accumulation of alpha chain and inclusion bodies in bone marrow erythroid progenitor cells. Failure to remove these bodies from the cell impairs cellular development, which ultimately leads to cellular destruction in bone marrow and severe degrees of ineffective hematopoiesis. Thereby, anemia in patients with thalassemia major arises from two case scenarios of ineffective hematopoiesis and decreased lifetime of red blood cells. The patients contain large amounts of hemoglobin F (fetal hemoglobin) in red blood cells. A relative increase is detected in hemoglobin A2 due to normal synthesis of delta chain [7]. The present study attempted to assess cardiac complications in thalassemia major patients using serum ferritin level due to following reasons: high prevalence of thalassemia in Fars province and particularly in Jahrom City, thalassemia-related complication and increased mortality rates followed by these complications and limited healthcare centers with inadequate supplies for most of these patients. The present study sought to find a fast route to diagnose cardiac complications at early stage and develop preventive measures since cardiac complication is one of the most common causes of deaths in patients with thalassemia major. Early detection of these complications at early stage can reduce mortality rates in these patients.

**METHOD**

This was a descriptive, cross-sectional study on 130 patients with thalassemia major in Cooley’s Center in Motahari Hospital in Jahrom. Total number of patients in this center was 167 among which 27 patients had thalassemia intermedia and 10 patients had sickle-thal. Therefore, these 37 patients were excluded from the study to eliminate the effect of confounding factors. Ultimately, 130 patients with thalassemia major were selected for the study. Serum ferritin levels was measured in laboratory of Motahari Hospital for 3 months. Echocardiography was simultaneously performed in Eco Center of the hospital. Age and gender of the patients were collected from patients’ records. Echocardiographic data including left ventricular contractility, the degree of left ventricular dilation, pulmonary hypertension, presence or absence of pericardial effusion and valve regurgitation was also collected. The collected data was delivered to statistics department in Jahrom University of Medicine for classification and comparison and statistical analysis. Echocardiographic findings were monitored in the study. A high percentage of patients with thalassemia major suffered from multiple degrees of valvular disorders such as mitral valve regurgitation and tricuspid valve regurgitation. Since valvular disorder is a representative of heart failure, serum ferritin level was assessed in these patients. Statistical analysis was performed using SPSS 17, t-test and ANOVA.

**RESULTS**

Of 130 patients with thalassemia major in Cooly’s Center in Motahari Hospital in Jahrom, 64 patients (48.22%) were males and 66 were females (51.78%). Moreover, 25 patients were from 1 to 10 years old (19.20%), 79 patients were from 11 to 21 years old (60.76%), 16 patients were from 22 to 32 years old (12.30%) and 10 patients were from 33 to 43 years old (7.74%). In this study, no statistically significant relationship was found between age and gender.

In our study, 15 patients experienced pulmonary hypertension among 130 patients with thalassemia major (mean age = 15.73). No trace of pulmonary hypertension was detected in remaining 115 patients.

Two patients suffered from impaired left ventricular contractility (1.53%, mean age = 21.50) among 130 patients with thalassemia major. No trace of impairment was found in remaining 128 patients. No statistically significant relationship was found between impaired left ventricular contractility and age.

In this study, 69 patients (53.08%) experienced mitral valve regurgitation among 130 patients with thalassemia major (mean age = 16.38). No evidence of mitral valve regurgitation was detected in remaining 61 patients (46.92%). No statistically significant relationship was found between mitral valve regurgitation and age.

In this study, 80 patients (61.54%) experienced tricuspid valve regurgitation among 130 patients with thalassemia major (mean age = 16.65). No trace of tricuspid valve regurgitation was found in remaining 50 patients (38.46%). In this study, no statistically significant relationship between age and tricuspid valve regurgitation.
No impairment was detected in left ventricular contractility in 28 patients with serum ferritin level less than 1000 ng/ml among 130 patients with thalassemia major. However, two patients suffered from impaired left ventricular contractility among those with serum ferritin level greater than 1000 ng/ml (n = 102). In this study, no significantly relationship was found between serum ferritin level and impaired left ventricular contractility (Table 1).

In this study, 17 patients (60.71%) experienced mitral valve regurgitation in those with serum ferritin level < 1000 ng/ml (n = 28) while 52 patients experienced mitral valve regurgitation in those with serum ferritin level > 1000 ng/ml (n = 102). In this study, no statistically significant relationship was found between serum ferritin level and mitral valve regurgitation (P = 0.66).

In this study, 14 patients (60.71%) developed tricuspid valve regurgitation in those with serum ferritin level less than 1000 ng/ml (n = 28) while 66 patients developed tricuspid valve regurgitation in those with serum ferritin level greater than 1000 ng/ml (n = 102). In this study, no statistically significant relationship was found between serum ferritin level and tricuspid valve regurgitation (P = 0.059) (Table 2).

In this study, 6 patients (60.71%) developed pulmonary hypertension in those with serum ferritin level less than 1000 ng/ml (n = 28) while 9 patients developed pulmonary hypertension in those with serum ferritin level greater than 1000 ng/ml (n = 102). In this study, no statistically significant relationship was found between serum ferritin level and pulmonary hypertension (P = 0.21).

In this study, no trace of left ventricular dilation was found in those with serum ferritin level less than 1000 ng/ml (n = 28) while one patient developed left ventricular dilation in those with serum ferritin level greater than 1000 ng/ml (n = 102). In this study, no statistically significant relationship was found between serum ferritin level and left ventricular dilation (P = 0.30) (Table 3).

**DISCUSSION**

Thalassemia patients suffered from severe irreversible complications prior to 1960 before regular blood transfusions and progress in iron-chelating agents. These complications mainly threatened the patients in 20s and unfortunately led to death. Given the extensive advancement in iron-chelators in 2000, lifetime of the patients increased and some of them lived up to 35 years old. The results of a study showed that 50% of patients lived up to 35 years old and 83% of the patients lived until 20s [8]. In this study, 130 patients with thalassemia major visited Cooly’s Center in Motahari Hospital in Jahrom City. Of these patients, 48.22% were males and 51.78 were females (mean age = 16.14). Moreover, 25% of patients were from 1 to 10 years old, 79% were from 11 to 21 years old, 16% were from 22 to 32 years old and 10% were from 33 to 43 years old. Female patients older than 33 were double the number of male patients older than 33 (7.70% versus 23%).

The risk of heart failure increased with increased lifetime of thalassemia patients. In 1964, 63% of thalassemia patients suffered from heart failure (mean age = 16). However, the incidence of heart failure has decreased in recent decades. Currently, this disease is diagnosed in 20-23 age group of thalassemia patients [9]. Three case of heart failure were detected in this study based on echocardiographic findings (1.53%, mean age = 21.50). This figure was close to international standards. Aessopos conducted a study in 2004 in which 2.5% of the patients

### Table 1: Comparison of serum ferritin level and impaired left ventricular contractility in patients with thalassemia major in Jahrom City in 2013

<table>
<thead>
<tr>
<th>Serum ferritin level</th>
<th>Number of cases</th>
<th>Impaired left ventricular contractility</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum ferritin level &lt; 1000</td>
<td>28</td>
<td>0</td>
</tr>
<tr>
<td>Serum ferritin level &gt; 1000</td>
<td>102</td>
<td>2 (1.07)</td>
</tr>
<tr>
<td>Total</td>
<td>130</td>
<td>2</td>
</tr>
</tbody>
</table>

### Table 2: Comparison of serum ferritin level and tricuspid valve regurgitation in patients with thalassemia major in Jahrom City in 2013

<table>
<thead>
<tr>
<th>Serum ferritin level</th>
<th>Number of cases</th>
<th>Tricuspid valve regurgitation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum ferritin level &lt; 1000</td>
<td>28</td>
<td>14 (50)</td>
</tr>
<tr>
<td>Serum ferritin level &gt; 1000</td>
<td>102</td>
<td>66 (64.60)</td>
</tr>
<tr>
<td>Total</td>
<td>130</td>
<td>80</td>
</tr>
</tbody>
</table>

### Table 3: Comparison of serum ferritin and left ventricular dilatation in patients with thalassemia major in Jahrom City in 2013

<table>
<thead>
<tr>
<th>Serum ferritin level</th>
<th>Number of cases</th>
<th>Left ventricular dilatation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum ferritin level &lt; 1000</td>
<td>28</td>
<td>0</td>
</tr>
<tr>
<td>Serum ferritin level &gt; 1000</td>
<td>102</td>
<td>1 (0.98)</td>
</tr>
<tr>
<td>Total</td>
<td>130</td>
<td>1</td>
</tr>
</tbody>
</table>
showed symptoms of congestive heart failure. Interestingly, the patients were older than 23. Reduced left ventricular contractility was also detected in those with left ventricular failure. Therefore, reduced left ventricular contractility can be used as a suitable criterion for prognosis of heart failure [10]. Roodpeima conducted a study on Tajrish Center and found out that 24% of patients (mean age = 16) suffered from heart failure [11]. Dilation (enlargement) of left ventricle can properly justify impairment in left ventricular contractility followed by heart failure [12]. In this study, one case of left ventricular dilatation was detected in echocardiographic findings (0.76%, mean age = 17) and the size of left ventricular was normal in other patients. Other cardiac complications such as iron overload and pericarditis were also taken into account. Although 21.5%-50% of thalassemia patients developed pericarditis in previous years [13], the incidence of this complication has decreased by 5% in recent years. A case of pericardial effusion was detected in this study (0.76%, mean age = 24). In recent years, some evidence of myocarditis was detected through biopsy. Myocarditis was associated with pericarditis in some cases. An evidence of involvement of a viral agent was also raised this case through PCR but the findings were not decisive. It is not acknowledged whether a viral agent or iron overload caused infiltration of inflammatory cells in myocardial tissue [13]. In this study, incidence of myocarditis was not assessed in patients with thalassemia major since biopsy was not available. Pulmonary arterial hypertension was another heart complication assessed in patients with thalassemia major in this study. It is the underlying cause of heart failure. Regular blood transfusions increases the risk of pulmonary arterial hypertension. Nevertheless, use of iron-chelating agents reduced the risk of hypoxia and increased pulmonary vascular resistance. Thereby, less cases of pulmonary arterial hypertension are expected in recent years [14]. In this study, only 15 patients developed pulmonary hypertension (11.54%, mean age = 15.88). Various studies have shown that 66% of patients with thalassemia major develop pulmonary arterial hypertension (mean age = 18) [14]. This figure was much lower in this study. Despite extensive treatment with iron-chelating agent, there was an ample evidence on cardiomyopathy associated with left ventricular dilatation followed by congestive heart failure and impaired left ventricular contractility. It was initially assumed that poor cooperation of the patients and misuse of iron-chelators led to development of cardiac complications. However, it should be noted that such iron-chelating agents as deferoxamine cannot alone prevent cardiovascular complications [10]. An evidence of cardiac complication can still be detected despite onset of treatment at young age. Thereby, serum ferritin level was introduced as an indicator of cardiac complication in thalassemia patients. Serum ferritin level is also a representative of iron overload. Is serum ferritin level associated with incidence of heart failure? This question was raised in this study. Moreover, 130 patients with thalassemia major were studied in Cooly’s Center in Motahari Hospital in Jahrom and divided into two groups.

Group I: those patients with serum ferritin level less than 1000 ng/ml (n = 28, 21.52% and mean age = 12.78). No trace of impaired left ventricular contractility was detected in this group.

Group II: those patients with serum ferritin level greater than 1000 ng/ml (n = 102, 78.48% and mean age = 16.67). Two cases of impaired left ventricular contractility was detected in echocardiographic findings (mean age = 21.50). No case of left ventricular dilatation was detected in Group I based on echocardiographic findings. On the other hand, one case of left ventricular dilatation was detected in Group II (0.98%, 22-32 age group). Mean serum ferritin level in thalassemia patients with impaired left ventricular contractility and left ventricular dilatation was 3740 ng/ml (mean age = 23.64). Statistical analysis showed that the relationship of serum ferritin level with left ventricular contractility and dilatation was not significant in these patients (P = 0.39). Yaprak et al. studied 63 patients with thalassemia major in Turkey using echocardiography. They showed that left ventricular diastolic dysfunction is clinically developed earlier than systolic dysfunction. They found no significant relationship between hematologic parameters such as mean serum ferritin level, maximum serum ferritin level, blood transfusion units and Doppler indicators left ventricular diastolic function [15]. Kermastinose also found no relationship between left ventricular diastolic dysfunction and serum ferritin level [12]. Aessoppos believed that serum ferritin level cannot be associated with left ventricular contractility. He found out that serum ferritin levels are still high in well-treated thalassemia patients with impaired left ventricular contractility. However, ferritin is an acute phase protein and cannot be used as a decisive factor in chronic cases such as left ventricular contractility [10]. No relationship was found between serum ferritin levels and impaired left ventricular contractility [11, 16]. Several factors in this study can elaborate why no relationship was found between these two factors. (a) Inadequate number of patients from a statistical perspective (n = 130). Larger sample is required to achieve more definitive results. (b) Mean age of the patients was 16.14. At this age, the risk of heart failure is not high. As mentioned earlier, impaired left ventricular contractility and left ventricular dilatation are developed at older age (mean = 33.64). (c) Ferritin is an acute phase protein, which is a suitable standard in acute cases rather than chronic cases such as
heart failure. This is because serum ferritin level changes in acute cases. (d) Vulvular disorders were detected in studied patients. These disorders can cause heart failure and impair left ventricular contractility. Therefore, it is necessary to exclude vulvular cases in future studies.

As mentioned earlier, valve insufficiency was also detected in some cases in addition to impaired left ventricular contractility. Of 130 patients, 69 patients (53.08%) experienced mitral valve regurgitation (mean age = 16.38). Prolonged mitral valve regurgitation can lead to heart failure. Therefore, the risk of heart failure increases in these patients. Comparison of serum ferritin levels showed 17 cases of mitral valve regurgitation (60.71%) in those patients with serum ferritin level less than 1000 ng/ml (n = 28) and 52 cases of mitral valve regurgitation (50.69%) in those patients with serum ferritin level greater than 1000 ng/ml (n = 102). However, no statistically significant relationship was found between serum ferritin level and mitral valve regurgitation (P = 0.66). It is not known why these patients experienced mitral valve regurgitation despite young age. Moreover, 14 cases of tricuspid valve regurgitation were detected (50%) in those patients with serum ferritin level less than 1000 ng/ml (n = 28) and 66 cases of tricuspid valve regurgitation (64.60%) were detected in those patients with serum ferritin level greater than 1000 ng/ml (n = 102). However, no statistically significant relationship was found between serum ferritin level and mitral valve regurgitation (P = 0.059). Given that iron overload cannot cause valve insufficiency, this disorder is independent of iron overload. Risk factors of valve insufficiency should be detected in order to prevent vulvular disorders and heart failure as prolonged valvular disorders cause heart failure.

CONCLUSION

According to the above-mentioned materials, 2.30% of patients developed some degrees of heart failure (mean serum ferritin level = 3740 ng/ml). However, no statistically significant relationship was found between serum ferritin levels and heart failure. This may be due to young age of the patients and small sample size that reduced the incidence of heart failure in studied population. Nevertheless, it seems that serum ferritin level should be closely monitored to prevent heart failure since serum ferritin levels were measured greater than 1000 ng/ml in the patients with heart failure.

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