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Comparison of Deferoxamine, Deferiprone and Deferasirox Iron-Chelating Agents in Reducing Serum Ferritin Levels in Patients with Thalassemia Major

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ABSTRACT

Aims Patients with thalassemia major suffer from iron overload due to excessive cell lysis. Iron-chelating agents are used to preventing the effects of iron overload on the body. Deferoxamine, deferiprone, and deferasirox are the most common iron-chelating agents. The aim of this study was to compare deferoxamine, deferiprone, and deferasirox iron-chelating agents in reducing serum ferritin levels in patients with thalassemia major.

Instrument & Methods This descriptive cross-sectional study was performed on 114 thalassemia major patients in the Cooley's ward of Shahid Beheshti Hospital, Yasuj, Iran, in 2018 who had been taking iron supplements for the past year. Census sampling was done. After recording patients' information, such as age, sex, and type of iron used, the blood sample was taken from the patients to measure serum ferritin and the results were analyzed using SPSS 22 software and multivariate analysis of variance.

Findings The mean serum ferritin level was 3438.70±2872.88 ng/ml. 14 patients were taking deferoxamine, 62 patients were using deferiprone, and 38 patients were consuming deferasirox. There was no significant difference between iron-chelating agents in reducing ferritin levels ($p>0.05$). Also, there was no significant difference between males and females in terms of decreased ferritin levels ($p>0.05$).

Conclusion There is no difference between deferoxamine, deferiprone and deferasirox iron-chelating agents in reducing the ferritin levels of patients with thalassemia and all can be administrated considering the cost, availability, condition, and patient's desire.

Keywords Thalassemia Major; Iron Chelating Agents; Deferoxamine; Deferiprone; Deferasirox; Ferritin

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Introduction

Thalassemia is a genetic disorder characterized by excessive lysis of red blood cells due to a defect in the hemoglobin beta chain and hemoglobin instability [1]. Most of the body's iron is in the hemoglobin, and in cases of the red blood cell lysis, the iron inside the hemoglobin is separated from the globin chain, and patients develop anemia or iron overload dependent on the type of lysis [2]. In general, intravascular hemolysis and extravascular hemolysis are two forms of red blood cell lysis [3]. In intravascular hemolysis, hemoglobin is lysed in the arteries, and as a result, the iron is excreted in the urine, and patients develop anemia, whereas, in extravascular hemolysis, iron is stored in lymphatic organs, such as the spleen and patients develop iron overload [3]. The red blood cells in thalassemia patients are subjected to extravascular hemolysis, and because the red blood cells are constantly lysing, these patients develop iron overload [4]. Increased iron ion load in patients with thalassemia, especially thalassemia major patients who are constantly receiving blood units leads to the deposition of iron ions in various organs, such as the heart, liver, kidneys, thyroid, and parathyroid glands resulting in a defect in the function of these organs [5, 6]. Iron deposition in the heart causes heart failure, such as cardiomyopathy or in the liver causes liver cirrhosis, which can be prevented by reducing the iron ions load in thalassemia patients [7]. Iron-chelating agents are used to preventing these side effects [5]. It is essential to evaluate and control the serum ferritin level in health decisions to reduce the side effects of iron overload, and subsequently the costs on the health system. No study has yet been conducted suggesting the indication for prescribing these iron-chelating agents in different regarding age and gender, and also no study simultaneously had compared these three drugs on serum ferritin levels in patients with thalassemia. On the other hand, providing a regional database of thalassemia major patients can be helpful in order to take iron-chelating agents regularly and a tendency toward a certain type of iron-chelating agent to start taking the drug. This study was done to investigate serum ferritin levels and compare the effects of iron-chelating agents on serum ferritin levels in patients with thalassemia major in Yasuj, Iran, who have been taking one of the deferoxamine, deferiprone and deferasirox iron-chelating agents for the past year. Therefore, the aim of this study was to compare deferoxamine, deferiprone, and deferasirox iron-chelating agents in reducing serum ferritin levels in patients with thalassemia major.

Instrument and Methods

This descriptive cross-sectional study was performed on 114 thalassemia major patients in the Cooley's ward of Shahid Beheshti Hospital, Yasuj, Iran, in 2018 who had been taking iron supplements for the past year. Census sampling was done and all patients with thalassemia (120 patients) who have been referring to the Cooley's ward of Yasuj Hospitals to receive one or two red blood cell units monthly were included. Patients have been taking one of three iron-chelating agents of deferoxamine, deferiprone, and deferasirox, and 1 mg of folic acid daily.

Inclusion criteria included regular intake of one of the three iron-chelating agents of deferoxamine, deferiprone, and deferasirox, no history of cardiovascular disease, liver disease, inflammatory diseases, and chronic kidney disease.

Finally, 114 eligible patients were included in the study. Six patients were excluded as they did not take iron-chelating agents properly, or their ferritin levels showed 2 standard deviations higher than the normal population, indicating that patients did not take regular chelating agents properly.

After obtaining conscious consent and determining the age, sex, and type of used iron-chelating agents (deferasirox, deferiprone, and deferoxamine), a blood sample was taken from the patients. The samples were then sent to a laboratory to measure serum ferritin levels. To measure ferritin, the Advia 30 hematology analyzer (Siemens; Germany) and the FERRITIN 250T CENTAUR kit (Siemens; Germany) were used.

SPSS 22 software and multivariate analysis of variance were used to analyze the data.

Findings

Of a total of 114 patients, 53 patients (46.5%) were male and 61 patients (53.5%) were female. The age range of the patients was 3-38 years with the mean age of was 20.56±8.03 years old.

The average ferritin level was 3438.70±2872.88 ng/ml and 51.7% of the patients had a ferritin level of <2500 ng/ml and 48.2% had a ferritin level of >2500 ng/ml (Table 1).

Among the patients, 14 cases reported using deferoxamine, 62 cases deferiprone, and 38 cases deferasirox.

There was no significant difference between iron-chelating agents in reducing ferritin levels ($p>0.05$). Also, there was no significant difference between male and female patients in terms of ferritin levels ($p>0.05$; Table 2).

Table 1) The absolute and relative frequency of patients according to serum ferritin level (n=114)

Ferritin level (ng/ml)	**No.**	**%**
Lower than 1000	26	22.8
1000-2500	33	28.9
Over 2500	55	48.2

Table 2) Comparison of the mean ferritin levels (ng/ml) according to sex and the type of iron-chelating agents

Variables	**Mean ferritin levels**	**P. value**
Gender		
Male	3282.23±2725.54	0.51
Female	3574.65±3010.90	
Iron-chelating agents		
Deferoxamine	2867.63±2623.57	
Deferiprone	3647.35±3071.09	0.44
Deferasirox	3308.68±2650.49	

Discussion

This research was the first study to compare serum ferritin levels in patients with thalassemia major who have routinely been taking one of the three iron-chelating agents of deferoxamine, deferiprone, or deferasirox. Of the 114 eligible patients, 14 cases reported using deferoxamine, 62 cases deferiprone, and 38 cases deferasirox.

In this study, the majority of patients reported using deferiprone, whereas deferoxamine was less common. After deferiprone, deferasirox was the most used drug. Considering the cost, difficulty of injection, and availability, our study was similar to other studies, as deferiprone was more popular due to its oral administration, availability, and cost-effectiveness. To administrate an iron-chelating agent in a patient at the risk of increased iron load, various factors, such as regional experience, availability, cost, patient's age, patient's cooperation, side effects of the drug, patient's preferences, especially distance (depending on whether the drug is injected or taken orally) should be considered to choose the drug [11, 12]. For example, in terms of cost, deferiprone is less expensive and more available than deferasirox, which has led to its more uses than the other two drugs [13]. Taher *et al*. in 2010 examined the satisfaction and ease of use of deferasirox with deferoxamine (desferal) among 237 patients and found that patients preferred deferasirox to desferal because of its ease of administration and no need for injection [14].

In patients with thalassemia, taking iron-chelating agents should be started when the ferritin level reaches more than 1000 ng/ml, which usually begins two years after treatment with blood unit transfusion [15]. Deferoxamine at a single dose should be taken by slow intravenous injection when patients develop acute complications due to iron overload. However, deferoxamine is also taken in the case with chronic iron overload at a dose of 4-50 mg/kg per day for 8-12 hours for 5 to 7 days. Deferoxamine should be adjusted in patients with renal insufficiency, but not in patients with hepatic impairment. However, the administration of deferoxamine may be associated with side effects, such as hives, hot flashes, hypotension, and shock, which are less common in oral forms of iron-chelating agents [16]. Deferiprone, administered orally at a dose of 25 mg/kg three times a day, does not require dose adjustment in cases with renal or hepatic insufficiency. However, there is a risk of bone marrow suppression and neutropenia and should be discontinued if neutropenia occurs [17]. Deferasirox is another oral iron-chelating agent that is given at a dose of 20 mg/kg per day and should be adjusted for cases with renal and hepatic insufficiency and also in cases with severe liver and kidney failure, it should not be prescribed. However, it is prescribed once a day, which is an advantage over two other types [18].

Considering the average level of target ferritin in thalassemia patients, studies have shown that the maximum ferritin level for reducing the overall side effects is 2500 ng/ml; however, it is better to be less than 1000 ng/ml to avoid the effects of increased iron load on the heart and prevent cardiomyopathy [19-21]. In this study, the overall average ferritin level in patients with thalassemia major was 3438 ng/ml and only half of the patients had a ferritin level of below 2500 ng/ml. By comparing the average ferritin level, which was relatively higher than the target level in various studies, and also that considering that half of the patients had higher ferritin levels than normal, it can be concluded that half of the patients did not receive appropriate control and follow-up and developing complications due to iron overload and failure of various organs are possible.

In this study, no statistically significant difference was observed between iron-chelating agents regarding serum ferritin levels. Several studies have been conducted on these agents but no study was found comparing these three agents. Maggio *et al*. compared deferoxamine and deferiprone in terms of decreasing ferritin levels, and there was no significant difference between the two drugs in terms of decreasing ferritin levels [22]. Murad *et al*. compared deferoxamine and deferoxamine in combination with deferiprone, both compounds reduced ferritin levels significantly when taken by patients for 12 months. However, there was no significant difference between the two groups in reducing ferritin levels [23]. Recently, another iron-chelating agent called Dexeroyx has been introduced that has not yet routinely entered the pharmaceutical market. In the study by Haji Gholami *et al*., who compared deferoxamine and this agent, no significant difference was observed in the reduction of serum ferritin levels between these two iron-chelating agents in thalassemia patients [24].

In this study, there was no association between sex and decreased serum ferritin levels following taking the iron-chelating agent. It was supposed that the average serum level may be lower in females due to the menstruation in female patients, but there was no statistically significant difference between the genders in serum ferritin. In a study by Borgna *et al*. after the discovery of deferoxamine, female thalassemia major patients born in the 1970s and older had lower mortality and morbidity than those born in the 1960s [25]. Hajigholami *et al*. compared the deferoxamine and dexeroyx iron-chelating agents and found no significant difference in the reduction of ferritin levels between these two agents in both sexes [24]

The study also had limitations; the study conditions, especially nutrition, which plays an important role in changes in patients' serum ferritin levels, were not controlled. Another limitation was the small sample size and differences between the numbers of samples

in the three groups treated with different iron-chelating agents.

Due to the limitations of the descriptive study and the small sample size, it is suggested that a comparison be made between the three drugs of deferoxamine, deferiprone, and deferasirox in future clinical trials study using larger sample size.

Conclusion

There is no difference between deferoxamine, deferiprone, and deferasirox iron-chelating agents in reducing the ferritin levels of patients with thalassemia and all can be administrated considering the cost, availability, condition, and patient's desire.

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Ethical Permission: This study was registered at the Research Ethics Committee of Yasouj University of Medical Sciences (IR.YUMS.REC.1397.109). The written consent was obtained from the participants.

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