Comparing the efficacy of Dexeroyx (Osveral) and Deferoxamine (Desferal) in reducing serum ferritin level in patients with thalassemia major

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Abstract

Background: Considering the necessity of permanent use of iron chelating agents in patients with thalassemia and the difficulty of using injectable drugs such as desferal, has given a special place to research on oral alternatives. The aim of the present study was to introduce oral Dexeroyx as an alternative to injectable desferal and also to determine its efficacy to reduce serum level of ferritin in patients with thalassemia.

Methods: This cross-over clinical trial was performed on 51 thalassemia patients randomly divided into two groups receiving desferal (50mg/kg/day intravenously) or Dexeroyx (20mg/kg/day orally). Serum ferritin levels were determined in both groups before treatment and then they were treated for 6 months and serum ferritin levels were determined on a monthly basis. After this period, with a one-month washout period, the treatment plan was transferred to the two groups.

Results: In the first phase of the study, although a downward trend in the level of ferritin was revealed in both groups within six months of interventions, no difference was found across the two groups. Similar findings were observed in the second phase of intervention so that in both groups receiving desferal or Dexeroyx, the serum level of ferritin gradually decreased within the six months of treatment, but no difference was found between the two groups in the trend of the change in ferritin level. The serum level of ferritin was independent to some baseline factors including gender, age, or history of splenectomy.

Conclusion: Dexeroyx is at least as effective as desferal in reducing serum ferritin levels. If there is no contraindication for using oral medications, Dexeroyx can be prescribed as an appropriate alternative for desferal in thalassemia patients.

Key words: Dexeroyx, Deferoxamine, serum ferritin level, thalassemia major

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Introduction

Thalassemia is a congenital homeopathic illness that appears in two major and minor forms (1). Because of anemia due to hemolysis, these patients are required to suffer repeated blood transfusions that lead to improved oxygen delivery to the tissues, as well as reduce ineffective hemorrhage and eliminate the symptoms of the disease. However, it may result in increasing the body's iron load which can cause early death especially before the age of 30 years (2,3). The ferritin serum level is the most widely used indicator for estimating body iron load (4). In today's world, many drugs are used to treat thalassemic patients, each with its own specific characteristics. These medications aim to reduce the load of excess iron or lower the level of serum ferritin in such patients. The only iron chelator currently available and approved is deferoxamine mesylate (desferal). But it is expensive and slightly absorbed by the digestive tract. Moreover, the method of binding this drug to iron requires its slow and prolonged infusion through the pump. The permanent presence of this drug in the body improves the function of the body and protects the tissues against toxic effects of iron released. Deferoxamine is almost non-toxic, however, cataracts, deafness and local skin reactions such as urticaria have been reported (5). Deferasirox is an iron-chelating agent with a completely different structure as compared to injectable desferal (6). The bioavailability of Dexeroyx in comparison to Desferal is 70%; it is metabolized in the liver and is available in tablets of 125, 250 and 500 mg (7). The starting dose of this drug is 20 mg/kg, taken once a day and half an hour before meals (8). Considering the necessity of permanent use of iron chelating agents in patients with thalassemia and the difficulty of using injectable drugs such as desferal which is used for this purpose, has given a special place to research new drugs that can control iron load in patients with thalassemia. The aim of the present study was to introduce oral Dexeroyx as an alternative to injectable desferal and also to determine its efficacy to reduce serum level of ferritin in patients with thalassemia.

Materials and Methods

This cross-over clinical trial was performed on Thalassemia patients after obtaining written informed consent and approval of the study process by Shahrekord University of Medical Sciences in 2011. All eligible patients were more than two years of age, had serum ferritin level higher than 100ng/dl, suffered more than 10 times blood transfusion with the volume of injected blood greater than 100 cc/kg. All patients had normal serum creatinine level (based on the amount of GFR in terms of weight and age), negative tests for HIV, or hepatitis viruses, normal hepatic enzyme levels (lower than five times normal level), normal CBC and platelet counts, normal cardiac function as left ventricular ejection fraction higher than 55% and left ventricular end diastolic volume less than 40cc/m. Also, none of the participants had visual or hearing problems. No evidence of renal defects (identified as proteinuria or Pr/Cr >0.6) was observed. Pregnant women or those in breastfeeding period were also not included. If the creatinine level was higher than the normal range or more than 33% higher than the baseline value within the study, the drug dose was halved and creatinine was monitored every week and thus in case of a progressive increase in creatinine, the drug was discontinued for one month; despite decreasing the dose of drug and the dosage of the medicine was reached at the initial level only, in case of normal creatinine. Those patients who faced heart diseases based on annual echocardiography, auditory and ocular problems during the annual examination, the positivity of hepatitis and HIV tests, or increasing liver enzymes more than 5 times of normal range were all excluded from the study. In case with pancytopenia, drugs were discontinued till normalizing the cell counts. In those with the appearance of severe nausea and vomiting, lack of response to antiemetic drugs or presence of skin rash, the dose of drug was reduced or even discontinued and after improvement of rashes, the drug was begun with a low dose and then gradually increased.

The patients were selected from thalassemic patients who referred to a private Thalassemia clinic in Shahrekord city and who were randomly divided into two groups receiving desferal (50mg/kg/day intravenously) or Dexeroyx (20mg/kg/day orally). Then the dosage of drugs was adjusted based on the number of received blood units and serum ferritin levels. Serum ferritin levels were determined in both groups before treatment and then they were treated for 6 months and serum ferritin levels were determined on a monthly basis. After this period, with a one-month washout period, the treatment plan was transferred to the two groups and for the first six months, the first group received Dexeroyx and the second group received desferal and then serum ferritin levels were re-measured monthly. Data were collected by questionnaire including age, gender, type and duration of the disease, as well as serum level of ferritin before and 6 months and one year after intervention.

The required sample size was determined as 30 patients in each group using the formula for estimating sample size for comparing the two means considering the variance of 46 and 25 for serum level of ferritin in the normal population and thalassemic individuals respectively, with the minimum between-group difference of 25%, with 95% confidence level and power of 80%.

Results were presented as mean ± standard deviation (SD) for quantitative variables and were summarized by absolute frequencies and percentages for categorical variables. Normality of data was analyzed using the Kolmogorov-Smirnoff test. Categorical variables were compared using chi-square test or Fisher's exact test when more than 20% of cells with expected count of less than 5 were observed. Quantitative variables were also compared with t test or Mann U test. The trend of the change in study parameters was assessed by the Repeated Measure ANOVA test. For the statistical analysis, the statistical software SPSS version 16.0 for windows (SPSS Inc., Chicago, IL) was used. P values of 0.05 or less were considered statistically significant.

Results

In total 51 patients (26 male and 25 female) were included into the study. The average age of the patients was 14.6 ± 6.9 years ranged 3 to 29 years and most of them (57%) were under 14 years of age. Also, 45.1% underwent splenectomy. Table 1 summarizes the serum level of ferritin within the first 6 months of intervention in both groups. There was no difference in baseline level of serum ferritin between the groups who received desferal or Dexeroyx (1356 ± 770ng/dl versus 1305 ± 515ng/dl, p = 0.79). In the first phase of the study, although a downward trend in the level of ferritin was revealed in both groups within six months of interventions, no difference was found across the two groups (Figure 1). Similar findings were observed in the second phase of intervention so that in both groups receiving desferal or Dexeroyx, the serum level of ferritin gradually decreased within the six months of treatment, but no difference was found between the two groups in the trend of the change in ferritin level (Table 2 and Figure 2). As shown in Table 3, the serum level of ferritin was independent to some baseline factors including gender, age, or history of splenectomy. In the age subgroup of 15 to 19 years, the serum level of ferritin increased after intervention probably due to the lack of appropriate use of medications by patients.

Table 1: Comparing serum ferritin level between the two groups during the first phase of the study

Group	Desferal (SD±Mean)	Dexeroyx (SD±Mean)	P value
Before intervention	1356 ± 770	1305 ± 515	0.79
1 month later	1239 ± 749	1217 ± 448	0.90
2 months later	1286 ± 497	1218 ± 436	0.61
3 months later	1157 ± 412	1226 ± 592	0.47
4 months later	1264 ± 494	1178 ± 310	0.47
5 months later	1195 ± 539	1193 ± 413	0.99
6 months later	1167 ± 487	1134 ± 286	0.79

Figure 1: Trend of the change in serum ferritin level within the first phase of intervention

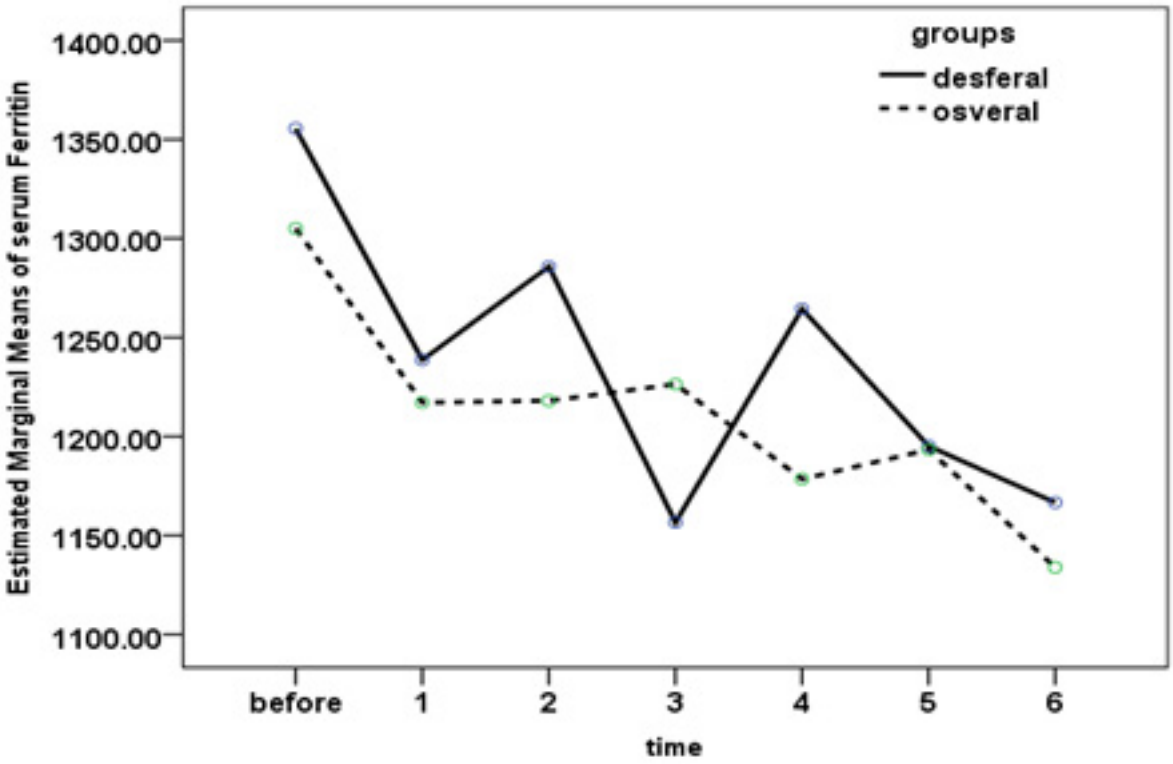

Table 2: Comparing serum ferritin level between the two groups during the second phase of the study

Group	Desferal (SD±Mean)	Dexeroyx (SD±Mean)	P value
1 month later	1125 ± 447	1132 ± 477	0.95
2 months later	1066 ± 423	1139 ± 453	0.55
3 months later	1028 ± 404	1125 ± 437	0.42
4 months later	977 ± 398	1002 ± 408	0.82
5 months later	946 ± 403	994 ± 398	0.67
6 months later	854 ± 389	988 ± 418	0.24

Figure 2: Trend of the change in serum ferritin level within the second phase of intervention

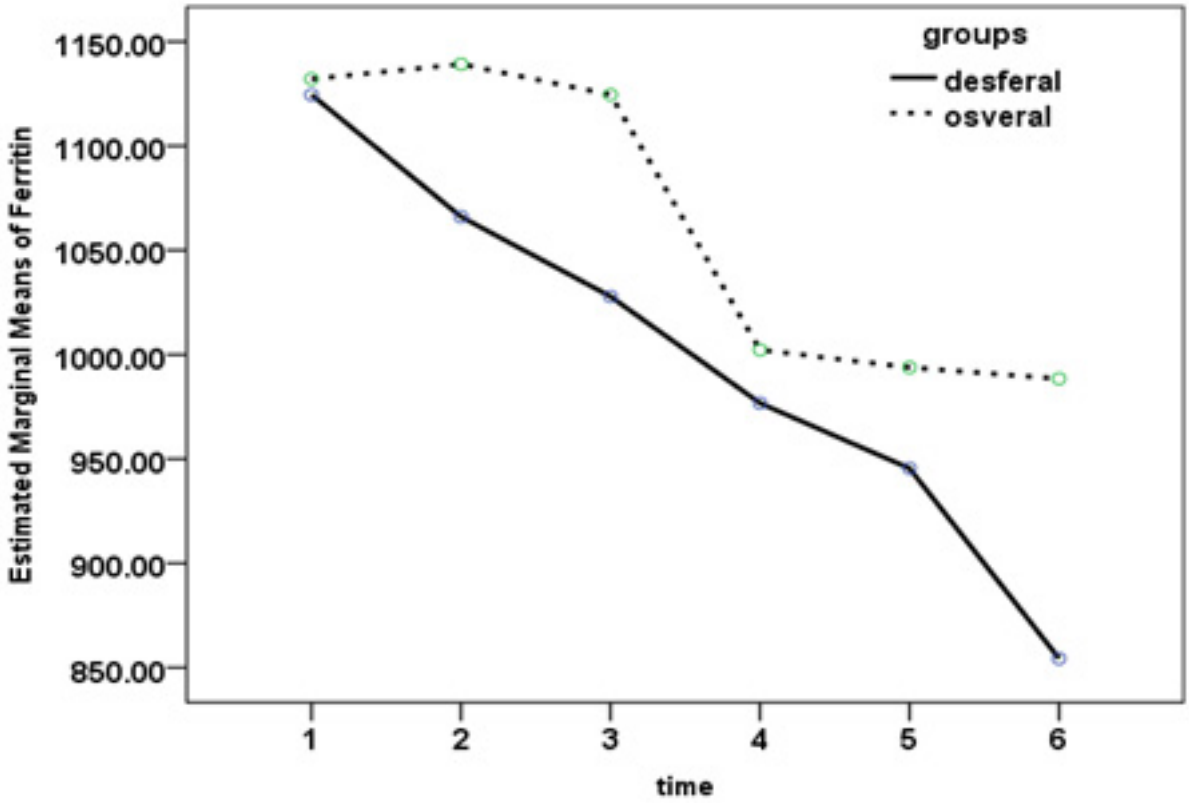

Table 3: mean serum level of ferritin within 12 months of intervention

Group	Before intervention	After intervention	Mean difference	P value
Drug				0.38
Desferal	1356 ± 770	854 ± 386	501 ± 154.3	
Dexeroyx	1305 ± 515	988 ± 418	317 ± 129.5	
Gender				0.21
Male	1226 ± 537	935 ± 313	502 ± 98.5	
Female	1444 ± 765	894 ± 484	907 ± 181.4	
Age subgroups				0.22
< 10 yr	1484 ± 616	745 ± 251	739 ± 153	
10 to 14 yr	1412 ± 963	1011 ± 418	401 ± 290	
15 to 19 yr	1061 ± 373	1064 ± 558	-2.8 ± 209	
20 to 24 yr	1299 ± 452	948 ± 451	351 ± 107	
≥ 25 yr	1179 ± 424	871 ± 337	307 ± 139	
Splenectomy				0.96
Yes	1325 ± 764	902 ± 483	831 ± 173	
No	1339 ± 577	926 ± 331	414 ± 125	

Discussion

According to the findings of this study, age and sex distribution of patients in both groups did not differ significantly. Also, history of splenectomy was not different in patients in both groups. Therefore, the confounding effect of the underlying variables including age, sex and history of splenectomy was neutralized in the two groups and therefore the observed differences between the two groups might be related to the effect of drugs. Also, this study was conducted as a cross-over trial. In fact, each patient was self-examined, and thus the results were believed to be reliable.

According to the results of this study, both desferal and Dexeroyx drugs had similar effects on serum ferritin levels in the studied patients. In this regard, administering desferal and Dexeroyx led to decreasing 501 ± 154.3 units and 317 ± 129.5 units in serum ferritin respectively. But according to the tests, the difference between the two groups was not significant. Several studies have been carried out on the effect of desferal on the reduction of serum ferritin level and the effect of this drug on reducing serum ferritin levels has been well proven in such studies. Nowadays, desferal is approved as a lowering sum ferritin level by the scientific communities and also by the FDA. In a study conducted by Pathare and his colleagues in Amman in 2010 (5), 19 patients with β thalassemia major were treated with Dexeroyx for 18 months indicating high efficacy of Dexeroyx in decreasing iron overload. The results of this study are close to our study results. In a study by Hoffbrand and colleagues (9) in order to investigate the effect of Dexeroyx on the reduction of blood iron levels in patients with thalassemia major in England, it was shown that the use of this oral drug can significantly affect the extraction of iron, which is in line with the results of this study. In a study conducted by Azizi et al (2010), 46 patients with thalassemia were treated with Dexeroyx for at least one year and showed that Dexeroyx is effective in reducing serum ferritin levels with no serious and dangerous side effects (10).

In a study by Molavi et al. (11), the effect of Dexeroyx in reducing serum iron levels was confirmed. In this study, 80 patients with thalassemia major were treated with oral Dexeroyx and patients were followed up for 1 year. In their study, serum ferritin levels decreased from 9494 ± 797 at the beginning of the study to 1578.78 ± 6.6 and the difference was significant before and after the treatment. Eshaghi et al. (12) also evaluated the administration of oral Dexeroyx in thalassemic patients and concluded that the drug could reduce serum ferritin levels. Fathi et al. (2017) showed that Dexeroyx had similar results with desferal in reducing ferritin serum levels, but after 12 months of the intervention, serum ferritin levels in patients who medicated with Dexeroyx decreased more as compared to ferritin levels in patients receiving desferal. Also, the use of Dexeroyx led to lower side effects when compared to the desferal group (13).

Regarding the results of the study and the significant reduction in serum ferritin level in patients with thalassemia, it can be concluded that Dexeroyx oral products are as effective as desferal in reducing serum iron levels. But because of the limited studies, especially the Iranian surveys, there is still no consensus on this finding emphasizing necessity for further studies.

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