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The Comparison of Desfonak with Desferal in Patients with Beta Thalassemia Major: A Randomized Crossover Clinical Trial

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Abstract

Background

Beta thalassemia (β-thalassemia) is one of the most common genetic disorders that reduces the amount of specific chain production in hemoglobin. The aim of this study was to compare the efficacy and safety of Desfonak with Desferal in patients with β-thalassemia major in Iran.

Materials and Methods

The study was a two-treatment and two-period crossover Randomized clinical trial design that was carried out on 100 thalassemic patients referred to Mohammad Kermanshahi hospital of Kermanshah city, Iran in 2018-19. Eligible patients were divided into two groups using a random number table (Group A, n=50; Group B, n=50). The group A received Desferal then Desfonak vs. (30 mg/kg in 8 h and 6 days in a week). The group B received Desfonak then Desferal. The data collection tool was a checklist, including variables of age, sex, AST, ALT, ferritin, urea, creatinine and different complications of gastrointestinal, articular, skin, respiratory system and hearing problems. The data were analyzed by STATA software (version 14.0).

Results

The results of the study showed that there are no significant statistical differences between Desferal and Desfonakin terms of different complications of GI, articular, skin, respiratory and hearing systems (P>0.05). Also, the results showed that there was no significant statistical difference between Desferal and Desfonak in terms of variables of AST, ALT, ferritin, urea and creatinine at two time periods (P>0.05).

Conclusion

The results of this study highlighted that Desfonak and Desferal have similar efficacy and safety in patients with thalassemia major.

Key Words: Crossover Design, Desfonak, Desferal, Thalassemia Major.

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1- INTRODUCTION

Beta thalassemia (β-thalassemia) is one of the most common genetic disorders that reduces the amount of specific chain production in hemoglobin (1). Severe thalassemia syndromes that are associated with severe anemia are commonly diagnosed early in childhood (2). Generally, inherited hemoglobin disorders such as thalassemia have worldwide distribution and its prevalence is different according to geographical area and ethnic groups (3). Thalassemia syndrome is common in the geographic regions of the Mediterranean, the Arabian Peninsula, parts of Africa, Iran, Turkey, India and Southeast Asia (4). In Iran, the North of the country has the highest prevalence of thalassemia gene, so that 11% of the population of Mazandaran province carry β-thalassemia gene and has the highest proportion of "thalassemic patients to population" in the country (5).

Major thalassemic patients are not able to produce sufficient amounts of hemoglobin, so that the disease manifests as severe anemia, so to deal with this problem the blood transfusion is necessary in these patients (6, 7).The lifetime dependence of thalassemic patients on repeated blood transfusions leads to increased iron load and its sedimentation in the body. So, the patients with β-thalassemia major due to chronic anemia and hypoxia, and also due to excess iron deposition in various organs, including the liver, heart, endocrine, and some other mechanisms, are affected by the disease (8, 9). Therefore, these repeated blood transfusions can lead to significant complications such as liver cirrhosis, cardiac disorders, diabetes, hypothyroidism, hypoparathyroidism, and hypogonadism (10). Since 1970, iron chelation therapy has been used to reduce iron overload in thalassemic patients (11-13). Deferoxamine (DFO, Desferal) is the oldest iron chelation which should be injected over 8-12 h subcutaneously (14-15). Desferal is considered to be the basis for the treatment of these patients by increasing the life expectancy of patients with β-thalassemia major to approximately 2-times.However, studies have shown that although deferoxamine can reduce the body's iron load, it may be associated with side effects such as skin complications, erythema, allergic reactions, bone pain and bone deformities, respiratory problems, growth retardation and in rare cases, hair loss, hearing loss, and tachycardia (16-19). Deferoxamine with Desferalbrand is imported in Iran. However, in the past few years, Iran has become self-sufficient in producing this drug and it produces Deferoxamine with Desfonak brand which has the same contents and characteristics of Desferal. The domestic production of this drug has a lot of dollar savings. Both medicines of Desferal and Desfonak are currently available to thalassemic patients by the Foundation of Special Diseases. However, there is no information available about the efficacy and side effects of Desfonak compared to Desferal and the field evidence relies on the complaints of thalassemic patients of side effects of Desfonak. Therefore, with regard to the above description, as well as the limited studies on the side effects of Desfonakin Iranian patients on the other hand, the aim of this study was to investigate the efficacy and side effects of Desfonak compared to Desferal in Iranian thalassemic patients.

2- MATERIALS AND METHODS

2-1. Study Design and Subjects

This study was performed as a randomized single-blind crossover clinical trial. This study was a two-treatment and two-period crossover design that was carried out on 100 thalassemic patients referred to Mohammad Kermanshahi hospital of Kermanshah city (Iran) in 2018-19. Inclusion criteria were as follows: β-thalassemia major with serum ferritin ≥1000 ng/ml (20), indication

of receipt of chelator and need of frequent blood transfusion and also exclusion criteria were as follows: the presence of kidney and liver failure, hypertension, skin diseases, respiratory and auditory diseases.

2-2. Sample Size

Previous studies have shown that the incidence of complications for Desferal and Desfonak is 5% and 20%, respectively. Considering that no study was found in this field, using the information provided by the pharmaceutical company, as well as the complaints of thalassemic patients in Kermanshahi hospital and based on the Alternative Dispute Resolution (ADR) forms that were collected during the 2 years before the study, the complications of the drugs to the above figure is estimated. Accordingly, the minimum sample size with 95% confidence level (CI) and 90% power was estimated to be 97. The calculation method and the formula used are as follows (Formula 1):

$$n = \frac{(z_{1-\frac{\alpha}{2}} + z_{1-\beta})^2 (p_1 q_1 + p_2 q_2)}{(p_1 - q_2)^2} \qquad n = \frac{(1/98 + 1/28)^2 [0.05(0.95) + 0.20(0.80)]}{(0.20 - 0.05)^2}$$

$$n = \frac{3.24^2 (0.2075)}{0.15^2} = 96.8 \cong 97$$

Formula.1: Sample Size Formula in Present Study.

2-3. Data Collection

In the present study, the data collection tool was a checklist, including the demographic and clinical variables of age, sex, Aspartate Aminotransferase (AST) test, Alanine aminotransferase (ALT) test, ferritin, urea , creatinine and also different complications of gastrointestinal (including nausea, diarrhea or abdominal pain), articular, skin (including itching, hives and skin rashes, redness or stiffness at the injection site), respiratory (including shortness of breath), and hearing systems (including tinnitus or hearing loss), lab tests were measured for both groups under study in 3 time periods including baseline, three months after first drug administration and three months after drug administration period. Patient's demographic information was recorded in the checklist by a researcher's assistance through the patient's records. To assess the laboratory tests, blood samples were taken from the patient in three steps (first and after receiving each drug), and the results were recorded in the checklist.

2-4. Intervention

This study was performed as a randomized single-blind crossover clinical trial. After obtaining informed consent from the participants, the eligible patients were divided into two groups using a random numbers table (Group A, n=50; Group B, n=50). Drugs were in the form of a 500 mg vial, each vial containing 5 ml distilled water. Drug prescription is 30 mg / kg administered as subcutaneous infusion in 8 h with a pump and 6 days a week. The group A received Desferal initially for 3 months, then the same group received Desfonak for another 3 months, in contrast, group B received Desfonak initially for 3 months then received Desferal for another 3 months. Then, the variables under study were measured for two group of A and B in 3 time periods including baseline (before intervention), the first trimester (after administration of Desferal for Group A and Desfonak for Group B), and the second trimester (after administration of Desfonak for Group A and Desferal for Group B) after intervention. **Figure.1** shows a general overview of cross-over design in the present study. **Figure.2** shows flow diagram for the subjects under study in this randomized crossover study. It should be noted that in the present study, regarding the 30-minute half-life of drugs and drug use for 6 days a week and the need forcontinued use of the drug, the washout period was applied between the 3-month period of the drugs for 24 h.

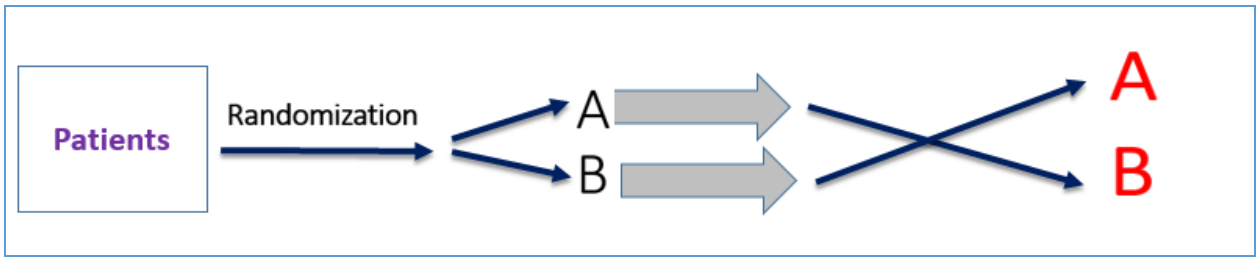

Fig.1: General Overview of Cross-Over Design in the present study.

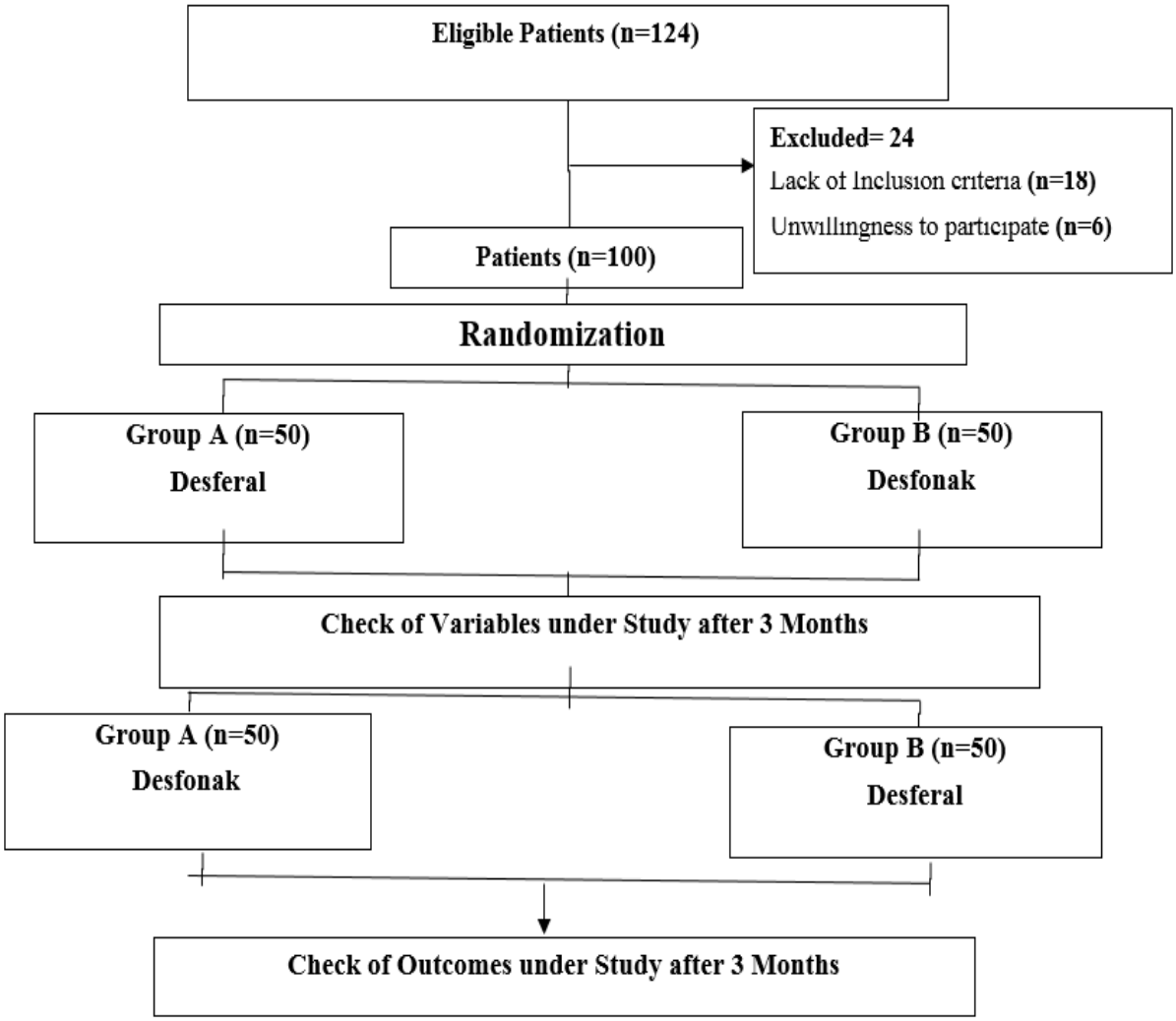

Fig.2: Flow Diagram for the subjects under study in this Randomized Crossover Design.

2-5. Ethical Considerations

Before the intervention, the objectives of the study were fully explained to the participants, then, if agreed, informed consent was obtained from them. In this study, all researchers were committed to the Helsinki Statement. This clinical trial study was approved by the Ethics Committee of Kermanshah University of Medical Sciences (ID-number: IR.KUMS.REC.1397.930). Also, it was registered in Iranian Registry of Clinical Trials (IRCTID: IRCT20130812014333N117).

2-6. Statistical Analysis

In this study, for the descriptive analysis, mean (standard deviation [SD]), and frequency (%) were used. Then, in inferential analysis, depending on the assumption of non-normality (according to Kolmogorov-Smirnov test), the independent-sample T-test or Mann–Whitney U test was used for comparing the means of the quantitative variables between two groups under study and also for comparison of the means of the these variables within two groups under study, depending on the assumption of non-normality (according to Kolmogorov-Smirnov test), the paired T-test or Wilcoxon Signed-Rank Test was applied. Also, for the qualitative variables in two groups under study Chi-square test was employed. It should be noted that the stata14 software was used for data analysis and P-value <0.05 was considered as a significant level.

3- RESULTS

This study was conducted on 100 patients with thalassemia major who referred to Mohammad Kermanshahi hospital of Kermanshah city (Iran) in 2018-19. The patients were randomly divided into the two groups of A (Desferal then Desfonak; n=50), and B (Desfonak then Desferal; n=50). **Table.1** shows baseline characteristics in two groups of A and B under study. The mean age of patients in the A and B groups under study were 26.36 ±7.23 and 26.26 ± 7.72 years, respectively. The number of males and females in A group was 20 (40%) vs. 30 (60%), and also for group B was 30 (60%) vs. 20 (40%). Generally, there were no significant statistical difference between the two groups under study in terms of baseline variables of age, sex, AST , ALT, ferritin, urea and creatinine (P>0.05). The lack of significant statistical difference between the two groups under study in terms of baseline variables can be a reason that randomization process has occurred correctly (**Table.1)**.

Table.2 presents the results of Chi-square test, which compared the side effects for Desferal and Desfonak. As can be seen, complications of gastrointestinal system (including nausea, diarrhea or abdominal pain) in two groups of Desferal and Desfonak were 2% vs. 1%, but this difference was not statistically significant (P>0.05). Also, the results of this test indicated that the complications of articular and complications of hearing system (including tinnitus or hearing loss) in two groups of Desferal and Desfonak were completely identical (P>0.05). Also, according to the complications of respiratory system (including shortness of breath), two groups of Desferal and Desfonak did not have significant statistical difference (1% vs. 2%) (P>0.05). Finally, the results of Chi-square test showed that the complications of skin (including itching, hives and skin rashes, redness or stiffness at the injection site) in two groups of Desferal and Desfonak were 10 (10%) and 15 (15%), respectively, as can be seen, although this difference was not statistically significant, but the incidence rate of skin complications in Desferal group was 5% lower than Desfonak group **(Table 2)**.

Table-1: Determination and Comparison of Baseline Variables in Two Groups of Desferal and Desfonak.

Quantitative Variables		Group	Number	Mean	SD	P-value
*Age (Year)		A***	50	26.36	7.23	0.817
		B****	50	26.26	7.72	
*AST (Aspartate aminotransferase)		A	50	34.52	17.44	0.931
		B	50	31.84	9.68	
*ALT (Alanine aminotransferase)		A	50	33.27	19.38	0.812
		B	50	30.82	8.90	
* Ferritin		A	50	2051.32	181.87	0.097
		B	50	2637.34	233.16	
**Urea		A	50	33.96	9.46	0.289
		B	50	32.18	7.07	
* Creatinine		A	50	0.75	0.22	0.798
		B	50	0.74	0.21	
Qualitative Variables		A		B		P-value
		Number	%	Number	%	
Sex of Patient	Male	20	40	30	60	0.056
	Female	30	60	20	40	

*: Mann–Whitney U Test.
**: Independent-Samples T-Test.
***Group A (Desferal then Desfonak).
****Group B (Desfonak then Desferal).

Table-2: Determination and Comparison of Side Effects of Desferal and Desfonak in patients under study (n=100).

Qualitative Variables		Desferal		Desfonak		P-value
		Number	%	Number	%	
*Complications of Gastrointestinal System	Yes	2	2	1	1	0.558
	No	98	98	99	99	
Complications of Articular	Yes	1	1	1	1	1.00
	No	99	99	99	99	
**Complications of Skin	Yes	10	10	15	15	0.248
	No	90	90	85	85	
***Complications of Respiratory problems	Yes	1	1	2	2	0.558
	No	99	99	98	98	
****Complications of Hearing system	Yes	1	1	1	1	1.00
	No	99	99	99	99	

*: Nausea, Diarrhea or Abdominal Pain.
**: Itching, Hives, Skin rashes, Redness or Stiffness at the Injection Site.
***: Shortness of Breath.
****: Tinnitus or Hearing Loss.

Table.3 shows the results of the Wilcoxon Signed-Rank test that were used to compare the mean of quantitative variables in two groups of Desferal and Desfonak at two time periods. As can be seen, the results of Wilcoxon Signed-Rank test that was applied to compare the means of quantitative variables in two groups of Desferal and Desfonak demonstrated that there is no significant statistical difference between two groups of Desferal and Desfonak under study in terms of variables of AST, ALT, ferritin, urea and creatinine at two time periods (P>0.05) **(Table.3)**.

Table-3: Determination and Comparison of the Means of Quantitative Variables for Desferal and Desfonak at two time periods

Time 1 (Period 1)	Variable	Group A		Group B	
		Desferal		Desfonak	
		Mean	S.D	Mean	S.D
The first three months	AST	31.60	16.73	30.96	8.83
	ALT	28.39	15.82	30.30	9.97
	Ferritin	1747.04	1046.83	2276.08	1419.01
	Urea	30.62	9.13	29.90	5.95
	Creatinine	0.73	0.19	0.67	0.15
Time 2 (Period 1)	Variable	Desfonak		Desferal	
		Mean	S.D	Mean	S.D
The second three months	AST	31.10	7.45	31.06	14.06
	ALT	31.54	8.58	30.11	16.22
	Ferritin	1521.30	904.86	2081.88	1333.98
	Urea	30.42	7.41	31.40	8.09
	Creatinine	0.74	0.14	0.73	0.15
P- value	AST	0.873		0.271	
	ALT	0.059		0.120	
	Ferritin	0.069		0.058	
	Urea	0.373		0.643	
	Creatinine	0.365		0.072	

SD: Standard deviation; AST: Aspartate aminotransferase; ALT: Alanine aminotransferase.

4- DISCUSSION

The aim of this study was to compare the efficacy and safety of Desfonak with Desferal in patients with β-thalassemia major in Iran. In recent years, the different pharmaceutical companies have produced Deferoxamine in the world. In Iran, Deferoxamine is also produced with Desfonak brand which has the same properties and content of Desferal. Food and Drug Administration (FDA) suggests that medical or toxicology researches are not for the multisource drug products (20). However, the prescription and consumption of new generic products by patients and physicians will be accepted with difficulty. Therefore, the implementation of appropriate clinical trial studies to assure patients and doctors of the efficacy of these new brands seems to be necessary. Hence, the aim of this study was to investigate the efficacy and side effects of Desfonak compared to Desferal in thalassemic patients referred to Mohammad Kermanshahi hospital of Kermanshah city (Iran). The results of this crossover study design showed that there are no significant statistical differences between Desferaland Desfonakin terms of different complications of gastrointestinal, articular, skin, respiratory and hearing systems (P>0.05). Also, the results of Wilcoxon Signed-Rank Test showed that there are no significant statistical differences between Desferal and

Desfonak in terms of variables of AST, ALT, ferritin, urea and creatinine at two time periods (P>0.05). According to our knowledge, the clinical trial studies that have been compared Desfonak with Desferal are very limited in Iran, so, we inevitably compare the results of this study with studies that are somewhat similar. The study by Eshghi et al. with the aim of comparing the efficacy and safety of a new Iranian generic (Desfonak) with the original brand product of Deferoxamine mesylate (Desferal) in Iranian patients, the results indicated that mean of urinary iron concentration for Desferal and Desfonak was 22.5±22.6 and 21.5±16.9 mg/m2, respectively and also mean of urinary iron excretion/Kg body weight for Desferal and Desfonak was 0.48±0.48 and 0.47±0.40 mg/m2, respectively. Finally, the same study concluded that two drugs Desferal and Desfonak did not have any significant statistical difference in terms of efficacy and safety (21).

Another study by Christoforidis et al., showed that combined treatment with Deferoxamine (DFO) and Deferiprone (DFP) can lead to significant decrease in serum ferritin and as well as a remarkable increase in excretion of iron from the urine (22). The study of Eshghi et al. indicated that two brands of Desferal and Desfonak do not have any significant statistical difference in terms of complications of hives and itchiness, irritation in injection place, headache, vomiting and nausea and other impositions (21). In a study by Abdelrazik with the aim of determining the efficacy and safety of a prospective alternating therapy with DFO and DFP in patients with β-thalassemia major and increased serum ferritin with DFO monotherapy alone, the results showed that the alternative therapy of DFO/DFP can significantly reduce ferritin serum and also led to remarkable improvement in myocardial performance in patients with β-thalassemia major. Therefore, the study suggested that combined treatment with DFO and DFP is more efficient and safe in comparison with monotherapy with DFP (23). The results of a study by Azarkeivan et al. to investigate the pulmonary abnormalities by pulmonary function test (PFT) in patients with β-thalassemia, demonstrated that there is a pulmonary dysfunction in patients with thalassemia major, which is most often seen in the form of a restricted pattern and can be directly related to the years of receiving blood transfusion (24). As you can see, the results of the study were consistent with the limited number of studies conducted in this area, however, due to the lack of studies that have directly compared the efficacy and safety of Desferal and Desfonak in Iran, the comparison was no longer possible and the authors of this study recommend doing more clinical trial studies in this field with higher sample sizes and more precision.

4-1. Limitations of the study

One of the strengths of this study, which should be mentioned is the type of randomized clinical trial (RCT) that we have used, which was crossover design. Because in this design, each patient acts as his (her) own control, as a result, many of the known and unknown confounding variables are adjusted, while it may be effective in comparison of the effects of two types of drugs in different groups.

5- CONCLUSION

The results of this study suggest that two brands of Desferal (original brand), and Desfonak (Iranian brand) do not have significant statistical difference in terms of different complications of gastrointestinal, articular, skin, respiratory and hearing systems. Also, these two drugs have similar effects on AST, ALT, ferritin, urea and creatinine of serum. Therefore, given that the similar efficacy and safety of these two drugs, physicians can prescribe Desfonak (Iranian brand) for patients with

thalassemia major and also the patients can consume this medicine without worry.

6- CONFLICT OF INTEREST: None.

7- ACKNOWLEDGMENT

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