



ORIGINAL ARTICLE

The Comparison of Efficacy of Original Brand Deferoxamine with Generic Iranian Made Deferoxamine in Urinary Iron Excretion in Patients with Thalassemia Major

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ABSTRACT

Background: Deferoxamine mesylate is still the conventional and well-known iron chelator for patients with thalassemia major. However, due to some marketing issues the well-known original brand, Desferal®, produced by Novartis Pharmaceuticals Company is not as available as before. The generic brands of Deferoxamine have been introduced in many parts of the world including Iran; however, they are not well accepted by the physicians and patients yet. This triple-blind randomized controlled trial was designed to compare the efficacy and safety of a new Iranian generic and the original brand product of Deferoxamine mesylate in Iranian patients.

Methods: The present Randomized triple-blind controlled trial research was carried on in nine centers throughout Iran. They were randomly divided into two similar groups and a Cross-over study was designed. 24-hour urine was collected after subcutaneous infusion of either drugs and urinary iron excretion was measured via atomic absorption spectrophotometer device. Acute adverse events during and after drug infusion were recorded. Mack Nara test and p-pair test were applied to compare two cross over interventions.

Results: 154 patients from 9 centers were enrolled in this study. There were 95 women and 59 men aged 6-34 years (mean age of 21.1years). Mean urinary iron concentration for Desferal (intervention A) vs. Desfonak (intervention B) groups was 22.5 ± 22.6 vs. 21.5 ± 16.9 mg/m², respectively. Mean urinary iron excretion/Kg body weight for Desferal (intervention A) vs. Desfonak (intervention B) groups was 0.48 ± 0.48 vs. 0.47 ± 0.40 mg/m², respectively.

Conclusion: According to the results of this study, there was similarity between efficacy and safety of the original and generic brands of deferoxamine (desferal vs. desfonak).

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Introduction

Humans have no intrinsic mechanism for excreting excess iron. Iron available for chelation is thought to be derived from the “labile iron pool”, and the size of this pool is directly related to the total body iron burden. It has been argued that irreversible tissue damage, particularly to the endocrine glands occurs at a very low iron burden during the first years of life.¹ Deferoxamine mesylate (DFO) is the first iron chelator which has got its FDA approval in 1970. With discovery of “Deferoxamine mesylate” in 1960, management of iron overload in patients with thalassemia major has developed extensively that this method of treatment became the traditional classic treatment of thalassemia major over the last half century

following the drug’s discovery.² DFO binds metal iron stoichiometrically, with a binding ratio of approximately 1:1 for deferoxamine to iron. DFO molecules enter the cells, bind iron molecules, and excrete in serum and bile as the product of feroxamine.³ The first original brand of DFO, Desferal® has been known well since 40 years ago and produced by Novartis Pharmaceuticals. During the last decade, after termination of its patent, DFO has been produced by other companies such as Bedford, Hospira, Watson lab, and App as generic products. Ronak pharmaceutical company (in Iran) has registered and produced DFO (Desfonak®) with the same contents and characteristics of DFO as Desferal®.

Generally, according to FDA principle of generic formulations, medical or toxicology studies are not required for the multisource drug products. Meanwhile, presenting the medical record for the medicinal product of self-evident used as fluid solution containing similar densities and excipient in comparable densities through injection into the vein, inside the muscles, subcutaneous or spinal space would not be necessary for registration of this new generic brand. However, new generic products are not as well accepted by the patients and physicians as the brand products among patients with thalassemia. However, new generic products are not as well accepted by patients and physicians as the brand products among patients with thalassemia.

On the other hand, new oral Iron chelator; deferasirox was available and well accepted at the time of the study due to its price and loss of enough experience in developing countries. All of the above mentioned issues led to loss of compliance

of the patients and caused serious complications. As a result, in addition to regular authority approval, a triple blind clinical trial seemed to be necessary to provide reassurance in patients and treating physicians. Due to shortage of time and limited research resources, it was decided to plan the study based on urinary iron excretion.

Taher and colleagues used urinary iron excretion and serum ferritin as markers for comparison between deferoxamine and deferiprone.⁴ A research accomplished by Boturao and co-workers showed that one of the non-invasive methods for evaluating the efficacy of deferoxamine mesylate would be “urinary iron concentration”.⁵ Christoforidis and colleagues showed that combination of desferal and deferiprone have 2.3 fold

increase in urine iron excretion compared to monotherapy with deferiprone.⁶ Rodrat and co-workers assessed urinary iron excretion for comparison of pharmacokinetics of two single doses of deferiprone in patients with thalassemia/hemoglobin E.⁷ We aimed to compare the therapeutic efficacy and adverse events of these two trade products of DFO based on urinary iron excretion of the both drugs.

Materials and Methods

The present triple-blind randomized controlled trial was carried out in 2010 in nine centers throughout Iran. The inclusion criteria were all children older than 2 years old who indicated to receive Deferoxamine as iron chelator and did not have any history of allergy or anaphylaxis to either drug if they were receiving before washout period. Exclusion criteria was defined as any history of allergy, anaphylaxis to the study drug or any contraindication to use it. The study was approved by ethics committee of Shahid Beheshti University of Medical Sciences. The inform consent was signed by the patients or their guardians.

154 patients with thalassemia major from nine centers were enrolled. They were divided into two groups according to the method of “Randomization balanced block” (figure 1), so a cross-over study was performed that everyone received both drugs in two occasions randomly. Both groups were in a washout period for 48 hours before starting the study, in a way that they did not take any iron chelator for that period of time. Then, either of the chelators were infused subcutaneously via a pump during a period of 8-10 hours as ordered by a physician according to their serum ferritin. The selection of the chelators was performed in a blind manner for two groups. 24-hour urine was collected from the beginning of the subcutaneous infusion of the iron chelator (desferal vs desfonac) and urinary iron was measured via atomic absorption spectrophotometry. This process was repeated

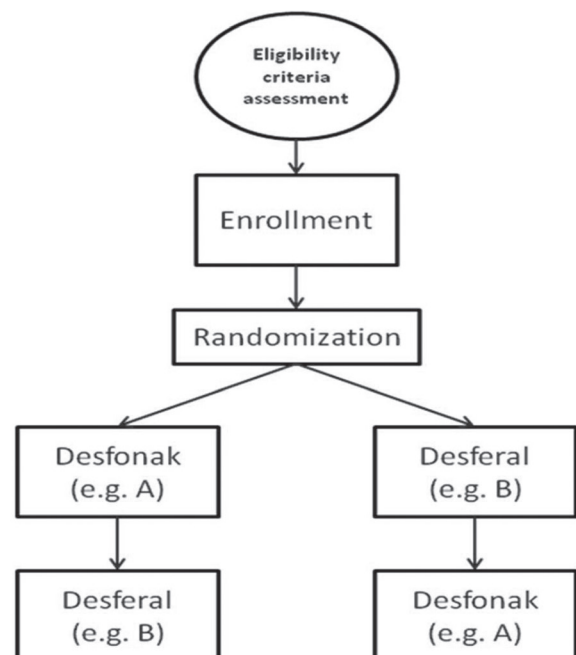


Figure 1: Cross randomization chart of the patients to receive the study pair drugs.

reciprocally for another brand in each group blindly after one month. Patients were supposed to inform their physicians or assistants by phone call in case of any change or imposition while referring to the hospital.

Statistical Analyses

Quantitative data are summarized as mean ± standard deviation and qualitative data are reported as frequency and percentages. Considering the type of the study (crossover study), Mack Nara test and paired t test was applied to compare two cross-over interventions. P values less than 0.05 were considered statistically significant.

Results

154 patients from 9 centers were enrolled in this study. There were 95 female and 59 male (6-34 years) (mean age of 21.1 years). 24-hour urinary iron concentration and the urine iron concentration per patient’s body weight are presented in figures 2 and 3. Due to the significant differences observed in the recorded side effects of Kerman center (figure 4) compared to the other centers, all the statistical analyses were done by removing the data of Kerman center. 80 women and 46 men within the age average of 21.5 years (6-34 years) were analyzed in this changed version of the study (figures 5 and 6, table 1).

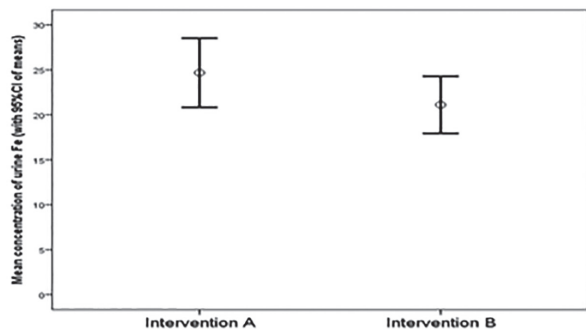


Figure 2: The comparison of 24-hour urinary iron concentration in 9 centers: Mean urinary iron concentration for desferal (intervention A) vs. desfonak (intervention B) groups was 22.5±22.6 vs. 21.5±16.9 (Log transformed data analysis result: P=0.97)

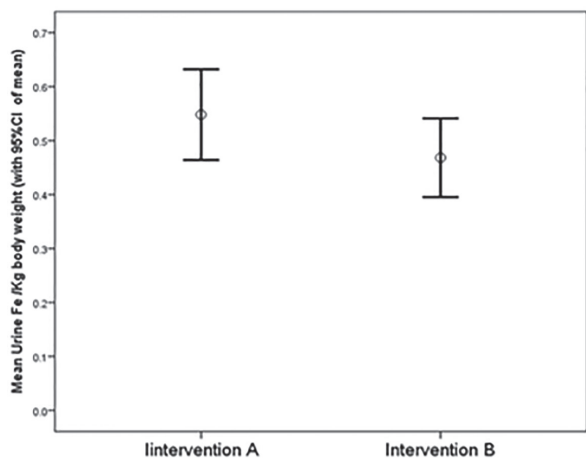


Figure 3: The comparison of urinary iron concentration/Kg body weight in 9 centers: Mean urinary iron/Kg body weight for desferal (intervention A) vs. desfonak (intervention B) groups was 0.48±0.48 vs. 0.47±0.40 (Log transformed data analysis result: P=0.90)

Discussion

The present study was the first to compare two brands of deferoxamine; Desferal® vs. Desfonak®. There are numerous studies in which the efficacy of iron chelation was assessed by measuring urinary iron excretion. Dubey and colleagues in an observational study on 21 children with thalassemia major discovered that subcutaneous infusion of deferoxamine could lead to increased iron

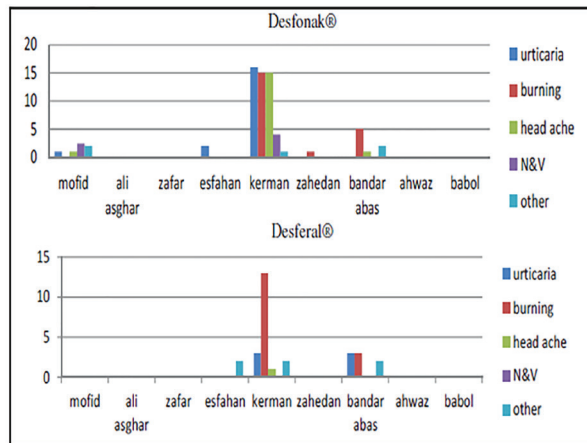


Figure 4: Side effects of Desferal vs. Desfonak in 9 centers

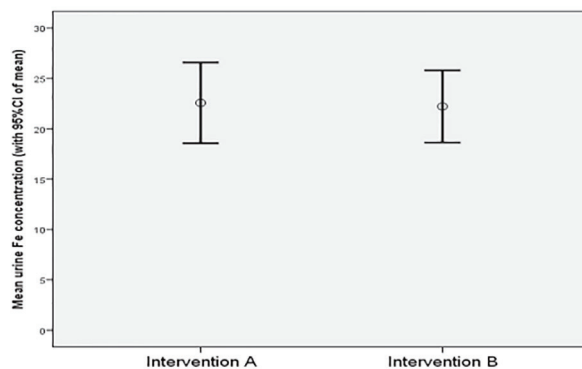


Figure 5: The comparison of 24-hour urinary iron concentration in 8 centers: Mean urinary iron concentration for desferal (intervention A) vs. desfonak (intervention B) groups was 25.2±24.2 vs. 21.6±20.0 (Log transformed data analysis result: P=0.06)

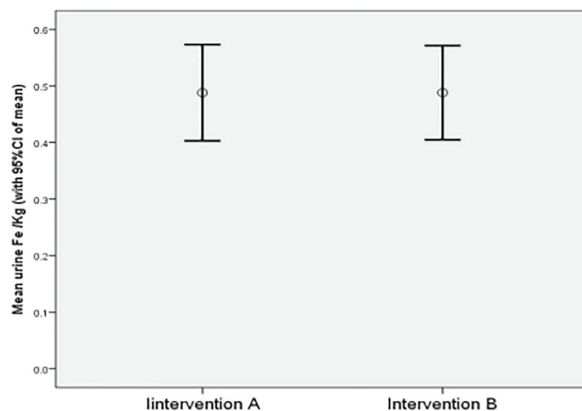


Figure 6: The comparison of urinary iron concentration/Kg body weight in 8 centers: Mean urinary iron/Kg body weight for desferal (intervention A) vs. desfonak (intervention B) groups was 0.56±0.53 vs. 0.48±0.46 (Log transformed data analysis result: P=0.05)

Table 1: Adverse events in 8 centers

		A type desferal	B type desfonak	P value (McNemar test)
1	Hives and itchiness	3 (2.4%)	3 (2.4%)	1.0
2	Irritation in injection place	3 (2.4%)	6 (4.8%)	0.45
3	Headache	0 (0%)	2 (1.6%)	0.50
4	Vomiting and nausea	0 (0%)	0 (0%)	1.0
5	Other impositions	4 (3.2%)	2 (1.6%)	0.63

excretion in urine.⁸ Similar results have been obtained by Fargion et al. on twenty-eight children with beta-thalassaemia major aged between 11 and 48 months.⁹ Christoforidis and colleagues studied the effects of different iron chelators (deferoxamine and deferiprone) and discovered that combined treatment with DFO and deferiprone (DFP) could result in significant decrease in serum ferritin and significant increase in urinary iron excretion.⁶ A study by Abdelrazik and colleagues was done on 600 patients with thalassemia with serum ferritin more than 2000 ng/dl using both DFP and DFO. Their efficacy was assessed by serum ferritin measurement, echocardiography and also urinary iron excretion during the period of the study. It was observed that combined treatment with DFO and DFP was more efficient in comparison with monotherapy with DFP ($P=0.001$).¹⁰

In our study, no significant difference in terms of efficacy and side effects

between the two groups was observed among 8 centers; however, more reports of hives and headache and less amounts of urinary iron excretion among patients from Kerman center who received Desfonak was reported. As mentioned before, the data from Kerman center caused significant difference in the analysis when were included in statistical analysis.

There was the possibility of loss of the blindness of the study in Kerman center. It might have been happened due to lack of a single staff to blind the study in all centers due to shortage of the time and budget and far distances. Meanwhile, other explanations such as physiologic and genetic difference between different populations could be considered as a probable mechanism for such a difference among data from Kerman center.

Conflict of Interest: None declared.

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