

Lens opacity as a serious side effect following chelation therapy in beta thalassemia: A comparison between deferoxamine and deferasirox; randomized double-blinded clinical trial

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Received: 29 October 2018

Accepted: 22 January 2019

Published: 28 February 2019

Keywords: Chelation therapy, Beta thalassemia, Deferasirox, deferoxamine

Abstract

Introduction: Ocular toxicity is a serious side effect following chelation therapy in patients suffering from major beta-thalassemia.

Objectives: We aimed to assess ocular toxicity (lens opacity) of the Iranian brand of deferasirox named "Osveral" marketed by an Iranian company and also to compare it with deferoxamine.

Patients and Methods: This randomized double-blinded clinical trial was performed on 50 major beta-thalassemia patients who were candidate for chelation therapy for the first time. Patients were randomly (using a computerized random number table) assigned to receive deferoxamine (50 mg/kg subcutaneous daily, 5 days per week, for 24 months) (25 patients) or Osveral (30 mg/kg orally for 24 months) (25 patients). After a year, patients were reassessed with regard to the appearance of lens opacity.

Results: In the group receiving deferoxamine, 4 patients (16.0%) suffered from mild opacity, 1 (4%) from moderate opacity and 2 (8%) from severe opacity, while in the group receiving Osveral, only 4 patients (16%) had mild lens opacity indicating no significant difference across the two groups ($P = 0.456$).

Conclusion: The rate of lens opacity appeared following administration of deferasirox and desferrioxamine is similar and in the range globally reported.

Citation: Golpayegani MR, Falahati V, abibollahi S, Fallahi M. Lens opacity as a serious side effect following chelation therapy in beta thalassemia: A comparison between deferoxamine and deferasirox; randomized double-blinded clinical trial. J Prev Epidemiol. 2019;4(1):e03.

Introduction

In major beta thalassemia, iron overload is a serious result of blood transition or increasing iron absorption through gastrointestinal (GI) system as the two events commonly revealed in such patients (1). In fact, in patients requiring blood transfusion therapy, it can be expected iron overload by overloading iron. However in non-transfusion dependent thalassemia, this overload occurred following a pathological condition as GI tract iron over absorption (2). Due to iron overload in patients and because of the toxic nature of iron, accumulation of iron in different tissues may lead to cellular toxicity and resultant multiple tissue failures such as heart and hepatic failure, hepatocellular carcinoma, endocrine abnormalities, and even growth retardation (3). To prevent, iron overload in thalassemia, the main approach is chelation therapy with the goal of increasing iron excretion in urine. However, balancing this process because of inhibiting excess chelation is an important point. In other

Core tip

In a randomized double-blinded clinical trial performed on 50 major beta-thalassemia patients who were candidate for chelation therapy, we found the rate of lens opacity appeared following administration of deferasirox and desferrioxamine is similar.

words, a key challenge of chelation therapy is to balance the benefits of chelation therapy with the unwanted effects of excessive chelation (4). In this regard, minute dose adjustment of chelators is essential to prevent excess chelation as well as to avoid reducing excessive iron levels and thus, balancing iron function at physiological level (5). In this regard, the tolerability of patients should be also considered.

Deferoxamine (Desferal) is a common iron chelator used since 1980 as subcutaneous infusions in beta thalassemia patients (6). The main mechanism of its action is to increase iron excretion through both renal and GI systems. The main advantages of



this medication are its short plasma half-life, rapidly elimination in bile and urine, and its dose-dependent effects on iron chelation. This drug can effectively maintain serum ferritin level in its normal range. Even by monotherapy, deferoxamine can control liver iron and hence total body iron stores. This drug can improve cardiac function by control of iron load in myocardium, and finally can improve patients' survival (7). However, some unwanted effects and limitations of these drugs include local skin reactions, local infection and even ulceration at the site of infusion due to requiring repeated intradermal infusion (8). Some systemic side effects of these drugs such as ocular toxicity have been described (9). In this regard, introducing oral form of chelators not only can create an appropriate condition to increase the patients' tolerability and level of satisfaction but also can prevent potential drug-related local side effects. Deferasirox is an oral iron chelator that was successfully trialed and approved by the United States Food and Drug Administration (FDA) in 2005 (10). It has been approved for those patients with chronic iron overload and requiring repeated blood transfusions, but its adverse side effects are now investigated.

Objectives

We aimed to assess ocular toxicity (lens opacity) of the Iranian brand of deferasirox named "Osveral" marketed by an Iranian company and also to compare it with desferrioxamine.

Patients and Methods

Study Design

This randomized double-blinded clinical trial was performed on 50 major beta thalassemia patients who were candidate for chelation therapy for the first time (Figure 1). The exclusion criteria were the history of any systemic disorders such as diabetes mellitus, rheumatic diseases, liver or renal problems or ocular disorders. Before intervention all subjects were examined by a single ophthalmologist regarding opacity of eye lens and thus those with this condition were all excluded from the study. Then, the patients were randomly (using a computerized random number Table) assigned to receive desferrioxamine (50 mg/kg subcutaneous daily, 5 days per week, for 24 months) (25 patients) or Osveral (30 mg/kg orally for 24 months) (25 patients). After a year, patients were reassessed with regard to the appearance of lens opacity by the same ophthalmologist and its severity was classified as mild, moderate, or severe. The probable side effects of the drugs were also checked.

Ethical issues

Human rights were respected in accordance with the Helsinki Declaration 1975, as revised in 1983. The ethical committee of Kermanshah University of Medical Sciences approved the study (Ethics No. P /7/711/1765/P). The informed consent was taken from the patients as well as from parents and first relatives. This paper was extracted

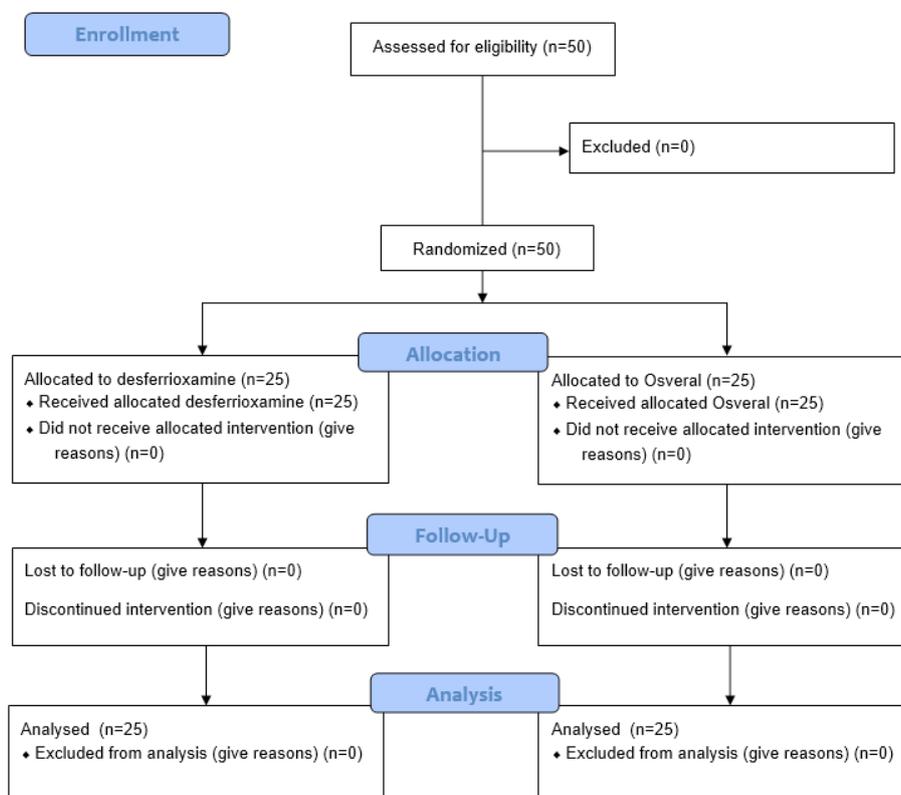


Figure 1. CONSORT (consolidated standards of reporting trial) chart for the study.

from the thesis of Vahid Falahati with number 281 in Kermanshah University of Medical Sciences. This study was also registered in the Iranian registry of clinical trial website (Identifier: IRCT201110087677N1; <https://irct.ir/trial/8139>)

Statistical analysis

For statistical analysis, results were presented as mean \pm standard deviation (SD) for quantitative variables and were summarized by absolute frequencies and percentages for categorical variables. Categorical variables were compared using chi-square test or Fisher's exact test when more than 20% of the cells with expected count of less than 5 were observed. 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

The two groups receiving desferrioxamine or Osveral were matched for male gender (48% versus 60%; *P* = 0.336) and all subjects in the age range of 2 to 14 years. Regarding family history of lens opacity, it was revealed in 16% of patients received desferrioxamine and 12% of those who received Osveral with no difference (*P* = 0.134). With respect to the appearance of lens opacity after a year of therapeutic interventions, in the group receiving desferrioxamine, 4 patients (16.0%) suffered from mild opacity, 1 (4%) from moderate opacity and 2 (8%) from severe opacity, while in the group receiving Osveral, only 4 patients (16%) had mild lens opacity indicating no significant difference across the two groups (*P* = 0.456). No adverse side effect was reported in both treatment groups. In Osveral group, no family history of lens opacity was revealed in those who suffering this complication, whereas a family history of lens opacity was found in one patient receiving desferrioxamine and suffering lens opacity.

Discussion

Although clinical safety of deferasirox has been described in comparison with desferrioxamine as a common

medication for chelation, the side effects of the two drugs especially ocular disturbances have been less assessed. As shown in the present trial, no difference was revealed in lens opacity between the two treatment schedule including desferrioxamine or deferasirox. Although the rate of lens opacity and its severity were observationally higher in those who received desferrioxamine, this difference was not statistically significant due to some reasons. First, small sample size of the study has been considered as a potential limitation leading to lowering study power. Thus, it might be resulted in insignificant difference between the trailed groups. However, the safety and clinical effectiveness of the two medications might be also similar as approved by different drug administrators. Overall, we think that the complication rate following administration of both drugs was notably high emphasizing appropriately titration of the drugs to minimize related side effects.

The clinical efficacy of desferrioxamine and deferasirox were examined in different trials and on different diseases subgroups. As shown by Vichinsky et al (11) on patients suffering sickle cell disease, adverse events most commonly associated with deferasirox were mild, including transient nausea, vomiting, diarrhea, abdominal pain and skin rash. Abnormal laboratory studies with deferasirox were occasionally associated with mild non-progressive increases in serum creatinine and reversible elevations in liver function tests. Although, in their study, those with ocular toxicity were all excluded and their statistics were all ignored. In total, our range obtained regarding lens opacity following administration of each of medications were in the global range among 9.3% to 44% (12). In a prospective non-controlled cohort study conducted by Dennerlein et al (13) to evaluate the presence of ocular side effects related to desferrioxamine, treatment, lens opacities were found in 41% that was higher than that obtained in our study. But in some other trials such as our observation no difference was found in lens opacity between desferrioxamine and deferasirox administration. In the study by Cappellini et al (14), early lens opacity was reported in the deferasirox core registration trials, but the incidence (0.3%) did not significantly differ from the control group of deferoxamine-treated patients.

Conclusion

In total, it seems that the rate of lens opacity following the two medications tested in the present trial was in the range obtained in other trials. However, no difference is expected in the occurrence of lens opacity between the two regimens.

Study limitations

During the research, we encountered some problems such as inconsistencies in implementation and time constraints. To achieve more reliable results, planning further studies with larger size and higher power is recommended.

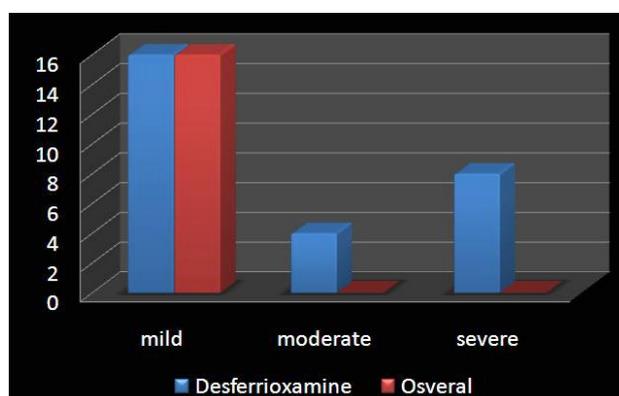


Figure 2. The rate of lens opacity in the groups treated with desferrioxamine and deferasirox.

Authors' contribution

MRG and VF designed the study, observed accuracy and validity of the study. SH collected the data and follow the study. MRG, VF, SH and MF supervised the project. GMR and VF wrote the paper. All authors edited and revised the final manuscript and accepted its publication.

Conflicts of interest

The authors declared no competing interests. The authors declare that the preference of one brand over other ones does not imply the bias of authors and it is only the result of authors' experiment.

Ethical considerations

Ethical issues (including plagiarism, data fabrication, double publication) have been completely observed by the authors.

Funding

None.

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