Ocular Complication and Visual Evoked Potential in β-Thalassemia Patients on Desferal Therapy


1Children's Medical Center Hospital, Tehran University of Medical Sciences, Tehran, Iran
2Dastgheib Hospital, Shiraz University of Medical Sciences, Iran
3Iranian Blood Transfusions Organization, Iran
4Amir-Al-Momenin Hospital Semnan University of Medical Sciences, Iran
5Semnan University of Medical Sciences, Iran
611 Moharam Hospital, Semnan University of Medical Sciences, Iran

Abstract: Major β-thalassemia is the most inherited hemoglobinopathy that caused severe and progressive anemia. Iron overload due to repeated blood transfusion cause organ damage such as heart, liver, endocrine gland and skeletal system. Desferal, as an iron chelator is used to eliminate iron from the blood that despite its side effects is few, ophthalmic toxicity due to it is exactly known. Eighty six major β-thalassemia, 10-35 years old selected 51 females and 35 males. They used desferoxamine regularly >5 years 3-6 times/week subcutaneously. Patients information filled in a questionnaire and then ophthalmologic examination was done. Likewise, personal and familial history of ophthalmic diseases has recorded and finally Visual Evoked Potential (VEP) by procedure of pattern reversal has been done for all patients. In 9 patients (10.5%) some symptoms as to desferal toxicity have been found that included: Abnormal VEP in 3 patients, macular pigmentation in 3 patients, color vision disorder in 2 patients (green and red colors) and cataract in one patient. These patients didn’t have any ophthalmic complaints. The age of starting to use desferal in this 9 patients was lower than others (3.3±3.8 years, p = 0.03), but there was no difference in age, desferal dose, weight, average of ferritin, splenectomy, heart disease and diabetes mellitus between these patients and others. Ophthalmic complications of desferoxamine in >10 years in age patients are lower than other areas in the world, but VEP can not be used as a screen test in this area contrary to other places. Also, desferal is an effective and low risk with very low risk/benefit ratio that is recommended to use regularly and to be under regulation and modification on base of serum ferritin.

Key words: Thalassemia, desferoxamine, ophthalmic complications, visual evoked potential

INTRODUCTION

Thalassemia is a familial anemia. These patients need regular blood transfusion throughout the life (Cappellini and Piga, 2008; Angelucci et al., 2008; Azarkeivan et al., 2009; Taher et al., 2006; Mehrvar et al., 2008; NOVARTIS, 1998). Iron overload due to repeated blood transfusion cause organ damage such as heart, liver, endocrine gland and skeletal system (Cappellini and Piga, 2008; Azarkeivan et al., 2009; Mehrvar et al., 2008; Economou et al., 2006). Many iron chelator approved such as desferoxamine, deferiprone and deferasirox. Desferoxamine is oldest and standard iron chelator that approved about 45 years ago. Desferoxamine caused profound changes in quality of life, mortality and morbidity (Taher et al., 2006; Mehrvar et al., 2008). The side effects of this drug are usually few and its risk/benefit is very low. However, visual and auditory effects, growth disorder and some infections are completely known (Zafeiriou et al., 2004). The visual effects of Desferoxamine that are made by high dose and sustained using of it are included: cataract, defect of the level and the field of vision, optic neuropathy, macular pigmentation and abnormal Visual Evoked Potential (VEP) (Marciani et al., 1991; Gelmi et al., 1988). Studies have shown recovery in symptoms after discontinuation of drug (Amabile et al., 1987). Other factors may be caused neural and visual disturbances in thalassemia include iron overload, chronic hypoxia due to anemia and zinc deficiency (Levine et al., 1997; Misulis and Spehlmann, 1994; Olivieri et al., 1986; Zafeiriou et al., 1998). This study was to perform VEP in

Corresponding Author: Mohammad Faranoush, Amir-Al-Momenin Hospital, Semnan University of Medical Sciences, Iran

928
transfusion dependent β-thalassemia for incidence and relationship of eye abnormalities to serum ferritin, the duration of using Desferal and desferrioxamine dosage.

**MATERIALS AND METHODS**

Eighty six transfusion dependent β-thalassemia were included. These patients were in regular blood transfusion, in order to maintain a pretransfusion hemoglobin level of 9-10 g dL⁻¹ and >10 years in age. They used Desferrioxamine (DFO) >5 years in 5-6 times/week subcutaneously. Informed consent were signed by patients or parents. They randomized in Dastghieb β-thalassemia clinic and data recorded from file that was included: age, gender, weight, the age of starting to use Desferal, the mean dose of Desferal (mg/kg/day), ferritin, the history of heart diseases, Diabetes mellitus, renal and liver status, splenectomy and other condition that cause nervous system damage.

Complete ophthalmologic examination have done for each patient that included visual acuity and field, color vision, papillary reaction, ocular pressure and anterior chamber examination by slit-lamp and fundoscopy and then the results have been recorded in their questionnaire.

In the later stage, VEP performed for all patients. VEP has been done in procedure of Pattern Reversal by Biomed 2008 electromyography instrument for both of eyes in every patient and the results were entered in special forms. VEP Procedure was as:

The patient lied in a calm and partly low light room in a fixed distance of T.V. that shows images and then by activating the electrode, the probe inserted in occipital, midfrontal and peritral parts of the patient's skull. Then, 200 optic stimulations are sent to the eye via the T.V and VEP waves are recorded. The recorded waves are included 4 waves: N1, P2, P1 and N2 that each of them has a partly fixed time delay. P1 wave is the most important of them and has about 100 milliseconds time delay. Increasing in this time delay is the marker of the optic nerve deficit, therefore, P1>100 milliseconds is supposed abnormal. It is noticeable that before doing VEP, visual refraction deficits should be omitted.

All patients had some test as a routine work-up that included blood glucose, ferritin, BUN, creatinine, AST, ALT, cholesterol, triglyceride and thyroid function test.

Statistical analysis were performed using student t-test, Chi-square, Fisher exact tests and Pearson correlation coefficient. The p<0.05 were considered stastically significant.

**RESULTS**

Fifty one patients (59.3%) were female and 35 patients (40.7%) of them were male. Mean±SD age of patients was 17.4±4.4 (10-35) years and also mean±SD weight were 39.3±9.1 (20-63) kg. Mean age at onset of blood transfusion was 0.6±0.4 years (0.4-1.3 years). Mean age at onset to use desferrioxamine was 5.0±3.5 years (0.8-18 years). The mean daily dose of DFO was 40.43±12.1 mg kg⁻¹ (28.4-66.7). Mean±SD serum ferritin was 2988.8±1258.7 ng mL⁻¹ (638-5960) (Table 1).

Splenectomy was performed in 17 (33.3%) female and 15 (42.9%) male patients. Cardiac complications like dilated cardiomyopathy, congestive heart failure and arrhythmia were in 15 female patients (29.4%) and 9 male patients (25.7%). Also, diabetes mellitus found in 4 (7.8%) female patients and 2 male patients (5.7%).

The past history of ophthalmic diseases was positive in 10 (11.7%) patient's that including amblyopia (2 cases), allergic conjunctivitis (2 cases) and refractive abnormalities (6 cases). Ocular problems had been observed in 18 female patients (35.3%) and 19 (54.3%) male patients. Theseocular abnormalities show in Table 2.

Other ophthalmic problems were in one male patient had scar of toxoplasmosis in iris. One male patient had iris distortion due to trauma and one female patient has corneal opacity due to using amiodarone and also one female patient has bilateral cataract, allergic conjunctivitis and Diabetes mellitus. There were not any cases of high ocular pressure and disorder of visual field.

Three patients had abnormal VEP (2 male, 1 female). These patients had not had any ocular complaint and any abnormalities in their ophthalmologic examination. There was abnormal VEP in one female patient of increasing the time delay in P1 wave (112.5 ms in the right eye and 114 ms in the left eye) and in one male patient of increasing the time delay in P1 wave (113 ms in the right eye and 114 ms in the left eye). Of course, in second case of abnormal VEP, it has been seen increasing the time delay in P2 wave too (231 ms in the right eye and 225 ms in the left eye). VEP was absolutely normal in 83 (96.5%) cases.

There was not a significant relation between the positive history of ophthalmic disorders and age, gender, weight, the age of starting to use Desferal, serum ferritin, splenectomy, heart diseases and DM.

There was not a significant relation between abnormal ophthalmologic examination in general and these factors (except splenectomy) too (p>0.05).
Contrary most of the other mentioned researches, the ophthalmic effects due to Desferal including acute, subacute effects and abnormal VEP are lower (9 cases or 10.4% in this research). Such as in Olivieri research 27%, in Triantafyllou research 26.6%, in Freedman research 22.5% of patients had ophthalmic Desferal toxicities (Olivieri et al., 1986; Zafeiricou et al., 1998; Wong et al., 1993; Triantafyllou et al., 1991; Bentur et al., 1990; Freedman et al., 1988; Taylor et al., 1987). Zafeiricou was the only almost similar research to this research and the ophthalmic effects in this research has been 15%, whereas, abnormal VEP in some researches was the only ophthalmic disorder due to using Desferal (100% in Zafeiricou research) and in others, has been the most current finding (80% in Freedman research; 79% in Olivieri research) (Economou et al., 2006; Zafeiricou et al., 1998; Olivieri et al., 1986; Triantafyllou et al., 1991). In present research, the spreading of the findings has been more, so the abnormal VEP has included 33.3% of the cases related to using desferal.

Other ophthalmic desferal complications were included 33.3%. Interesting, in none of 9 mentioned patients, it was not seen >1 finding, whereas, the most of the ophthalmic findings in other researches has been accompanied with abnormal VEP (Zafeiricou et al., 1998; Triantafyllou et al., 1991). One of the differentiated remarks of this research comparing to other mentioned researches is recording the different ophthalmic defects that have not already been related to using desferal or own thalassemia disease such as pinguecula and allergic conjunctivitis. The clinical importance of these findings is not exactly precise and needs to be under examined as case-control study for better evaluation.

Due to average serum ferritin in these patients (2988.8 mg/L), it seems that the iron chelation was not well in these patients and may be the ophthalmic complications are less than other research. We used lower doses of desferrioxamine (40.4 mg/day) comparing of other researches, for example: 70 mg/kg/day in Olivieri research (Olivieri et al., 1986) and 120 mg/kg/day in Levine research (Levine et al., 1997).
In present research like others in the world, there are not clinical symptoms due to Desferal toxicity accompanying abnormal VEP and ophthalmologic examination. As an example, in Zaferious research (Economou et al., 2006; Zaferious et al., 1998) and Taylor research (Taylor et al., 1987) like the research, none of these cases were symptomatic and in Freedman research (Freedman et al., 1988), 12% of the cases were not symptomatic. It seems that ophthalmic toxicity due to Desferal, regardless of every contributive factor like DFO dose and duration of using.

Relation of abnormal VEP with DFO dose, the duration of using is partly like Wong research (Wong et al., 1993) and Zaferious research and in opposite of Benture research, Olivieri research and Freedman research. It was only discussed about splenectomy and its relation to ophthalmic effects due to Desferal in Zaferious research that was not been like the findings of this research in this field. The macular pigmentation as one of the ophthalmic effects due to using Desferal, to the dose of drug, its duration of use and other factors has been like Olivieri research.

The color vision disorder that examined in the research as one of the side effects of Desferal, has only been researched in Olivieri et al. (1986) research (only one case with partial remission after stopping to use desferal) and the statistical information has not been observed in cases of Desferal dose, its using duration in other researches. So, it is important.

In this research, one case of cataract has been reported that can be due to desferal potentially. In other researches, there was not been observed any statistics in this regard (Zaferious et al., 1998; Karimi et al., 2002; Shamsian et al., 2008).

Significant relation of abnormal ophthalmologic examination (due to Desferal toxicity or not) with splenectomy that of course these variants can be the effects of thalassemia major itself and not only due to Desferal toxicity.

**CONCLUSION**

According to above findings, the iron chelation is not appropriate performed, on the other hand, the ophthalmic effects due to desferal toxicity is less than other world areas and is maximum 10.5%, because of using Desferal in lower doses.

Then, the ophthalmic Desferal toxicity in our study is rare. Also, low prevalence of abnormal VEP in these patients decreases the necessity as a routine work-up.

Attention that there is not any relation between the dose of Desferal and the incidence of ophthalmic symptoms, it is possible to increase the dose of Desferal in most of thalassemic patients to prevent the iron accumulation, but serum ferritin should be considered at the same time.

**ACKNOWLEDGEMENTS**

We would like to acknowledge, the valued assistance of personnel's of Dastgheib clinic and Research Vice Chancellor of Shiraz University of Medical Sciences.

**REFERENCES**


