Research Journal of Biological Sciences 4 (8): 928-932, 2009
ISSN: 1815-8846

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

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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 desferioxamine regularly >5 years 3-6 times/week subcutaneousely. 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 desferioxamine 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, desferioxamine, 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 desferioxamine, deferipirone and deferasirox. Desferioxamine is oldest and standard iron chelator that approved about 45 years ago. Desferioxamine 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 Desferioxamine 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

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transfusion dependent β-thalassemia for incidence and relationship of eye abnormalities to serum ferritin, the duration of using Desferal and desferioxamine 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 Desferioxamine (DFO) >5 years in 5-6 times/ week subcutaneousely. Informed consent were signed by patients or parents. They randomized in Dastgheib 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 parietal 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>110 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, cholestrol, 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 desferioxamine 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). Occular problems had been observed in 18 female patients (35.3%) and 19 (54.3%) male patients. These ocular 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 amiodaron 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 ($p>0.05$).

Table 1: Demographic data in thalassemia patients

Parameters	Mean±SD	Range
Age (years)	17.4±4.4	10-35
Age male (years)	18.65±4.72	12-35
Age female (years)	15.49±3.14	10-22
Weigth (kg)	39.3±9.08	20-63
Weigth male (kg)	37.83±10.56	20-63
Weigth female (kg)	40.35±7.84	21-55
Age onset of DFO (years)	5.00±3.50	0.8-18
DFO°doses (mg/kg/day)	40.43±12.1	28.4-66.7
Ferritin (ng mL^{-1})	2988.8±1258.7	638-5960
Ferritin male (ng mL^{-1})	2945.9±1327.5	726-5960
Ferritin female (ng mL^{-1})	3016.8±1221.9	638-5580

°DFO: Desferioxamine

Table 2: Occular finding in thalassemia

Occular abnormalities	Number	Male	Female
Allergic conjunctivitis	24 (27.9)	14 (40)	10 (19.6)
Pinguecula	10 (11.6)	1 (2.9)	9 (17.6)
Macullar pigmentation	3 (3.5)	2 (5.7)	1 (2)
Color vision abnormalities (green, red)	2 (2.3)	2 (5.7)	0 (0)
Belpharitis	2 (2.3)	2 (5.7)	0 (0)
Xeroophthalmia	6 (6.9)	1 (2.8)	5 (6.9)
Others	5 (5.6)	3 (8.7)	2 (4)

Values in parenthesis are percentage

Table 3: Comparing characteristics of ophthalmic desferal toxicity symptoms

	Desferal toxicity symptoms		
Variables	Positive n = 9	Negative n =77	p-value
Age (years)	16.6±4.9	17.5±4.4	>0.05
Weight (kg)	38.6±10.8	39.4±8.9	>0.05
Desferal starting age (years)	3.3±3.8	5.1±3.5	0.03
Desferal dose (mg/kg/day)	41.2±8.1	40.3±7.8	>0.05
Feritin (ng mL^{-1})	3002±1488	2940±1229.1	>0.05

However, there was significant relation between abnormal ophthalmologic examination and splenectomy ($p = 0.03$), but there was not significant relation between macular pigmentation and the mentioned factors above ($p>0.05$).

It has not also been seen significant relation between incidence of color vision disorders and these variables ($p>0.05$). Also, the significant relation has not been seen between dry eye and the mentioned variants ($p>0.05$), although, this relation has become significant in upper ages, but it is not significant statistically ($p = 0.057$) (Table 3).

It has not been observed any statistical significant relation between abnormal VEP and the above factors, also, with abnormal ophthalmologic examination such as: disorder of color vision, pingucola, macular pigmentation, dry eye, allergic conjunctivitis and belepharitis.

Three female patients and 6 male patients showed the signs and symptoms of Desferal toxicity which abnormal VEP was seen in 2 male patients and the disorder of color vision was seen in 2 male patients and macular pigmentation was seen in 2 male patients and one female patient and also bilateral cataract was seen in one female patient. None of the patients has >1 finding. Comparison between toxicity group and without toxicity was shown in Table 3.

In toxicity group, 3 patients have been done splenectomy, 2 patients have already had heart diseases and 2 patients have had DM with no significant relation with other signs and symptoms.

DISCUSSION

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 Traintafyllou research 26.6%, in Freedman research 22.5% of patients had ophthalmic Desferal toxicities (Olivieri *et al*., 1986; Zafeiriou *et al*., 1998; Wong *et al*., 1993; Triantafyllou *et al*., 1991; Bentur *et al*., 1990; Freedman *et al*., 1988; Taylor *et al*., 1987). Zafeirious research was the only almost similar research to this research and the ophthalmic effects in that research has been 15%, whereas, abnormal VEP in some researches was the only ophthalmic disorder due to using Desferal (100% in Zafeirious research) and in others, has been the most current finding (80% in Freedman research, 79% in Olivieri research) (Economou *et al*., 2006; Zafeiriou *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 (Zafeiriou *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 pingucola 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 ng mL^{-1}), 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 desferioxamine (40.43±7.58) 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 Zafeirious research (Economou *et al*., 2006; Zafeiriou *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 Zafeirious research and in opposite of Benture research, Oliviery research and Freedman research. It was only discussed about splenectomy and its relation to ophthalmic effects due to Desferal in Zafeirious 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 (Zafeiriou *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.

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