The assessment of the incidences of ocular toxicity and ocular findings caused by iron-chelating compound

La evaluación de las incidencias de toxicidad ocular y hallazgos oculares causados por el compuesto quelante de hierro

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Abstract

Introduction: The current article mainly attempts to evaluate the incidences of ocular toxicity and ocular findings stemming from the iron-chelating compound, deferasirox in patients with beta-thalassemia receiving recurrent blood transfusions. **Patients and methods:** Nearly sixty cases with ß-thalassemia major participated as case subjects, while an additional sixty otherwise healthy volunteers were engaged as control subjects. All of the subjects were age and sex-matched, and all of the volunteers were included as case subjects. **Results:** Despite the fact that all of the cases with beta-thalassemia did not have any signs or symptoms of eye disease, abnormal visual features (dry eye (35%), retinal pigment changes and retinal epithelium degeneration (15%), and ocular abnormalities (36.2%) were observed in 67% of thalassemia patients, indicating that the disease is not contagious, given the findings. The incidence of visual anomalies in the control group was 18.2 %, which was significantly subtler in comparison to thalassemia patients (P≤0.001). A non-significant link exists between ocular defects and serum ferritin (P=0.543) or blood hemoglobin (P=0.265). A statistically significant connection between the frequency of blood transfusions and ocular abnormalities was discovered (P=0.001). **Conclusion:** Based on the results, thalassemia patients should go through regular ophthalmological examination to detect early anomalies in their visual system when using an iron chelator.

Keywords: ocular toxicity, beta-thalassemia, blood transfusions, abnormal visual features.

Resumen

Introducción: El presente artículo intenta principalmente evaluar las incidencias de toxicidad ocular y los hallazgos oculares derivados del compuesto quelante de hierro deferasirox en pacientes con beta-talasemia que reciben transfusiones de sangre recurrentes. Pacientes y **métodos:** Casi sesenta casos con ß-talasemia mayor participaron como sujetos de casos, mientras que otros sesenta voluntarios sanos participaron como sujetos de control. Todos los sujetos tenían la misma edad y sexo, y todos los voluntarios se incluyeron como sujetos de casos. **Resultados:** Apesar de que todos los casos con beta-talasemia no tenían ningún signo o síntoma de enfermedad ocular, características visuales anormales (ojo seco (35%), cambios en la pigmentación retiniana y degeneración del epitelio retiniano (15%) y se observaron anomalías visuales (36,2%) en el 67% de los pacientes con talasemia, lo que indica que la enfermedad no es contagiosa, dados los hallazgos. La incidencia de anomalías visuales en el grupo control fue del 18,2 %, que fue significativamente más sutil en comparación con los pacientes con talasemia (P≤0,001). Existe una relación no significativa entre los defectos oculares y la ferritina sérica (P=0,543) o la hemoglobina en sangre (P=0,265). Se descubrió una conexión estadísticamente significativa entre la frecuencia de las transfusiones de sangre y las anomalías oculares (P=0,001) **Conclusión:** En base a los resultados, es recomendable que los pacientes con talasemia se realicen un examen oftalmológico periódico para detectar tempranamente anomalías en su sistema visual al utilizar un quelante de hierro.

Palabras clave: toxicidad ocular, beta-talasemia, transfusiones de sangre, características visuales anormales.

Introduction

A variety of symptoms, including blindness, can be experienced by people who have thalassemia, which is a severe genetic blood disorder that affects the whole body[1,2]. These patients' eye findings could be related to the thalassemic disorder, iron overload caused by regular blood transfusions, or iron chelator used to reduce the amount of iron stored in their bodies[3,4]. There have been numerous reports on the ocular complications of thalassemia as well as the therapeutic options available to treat these complications. [5]However, there have only been a few studies conducted on these patients to determine their contrast sensitivity. When patients have normal vision but poor contrast sensitivity, they can be identified

early in the course of their visual system abnormalities, even when the patient's vision is normal[6]. Symptoms of the disorder or as a side effect of iron chelation therapy may manifest themselves in the ophthalmologic system Renal function[1,7]. Angioid streaks, cataracts, retinal venous tortuosity (twisting of the retina), retinal toxicity (twisting of the retina), "retinal pigment epithelium (RPE)" erosion and "mottling", "optic neuropathy", and diminished "visual acuity" are all possible effects of this syndrome[8].

One of the core goals of this study was to assess the sensitivity to differences in contrast in multi transfused-thalassemia patients who were receiving oral deferasirox to that of healthy control subjects. The researchers also looked into the relationships between contrast detectability and serum ferritin concentration, the extent of blood transfusions, and the dosage of iron chelation therapy, among other things. Secondly, we wanted to find out how common ocular abnormalities were among patients who had received multiple transfusions of beta-thalassemia and what the relationship was between them, and their serum ferritin levels, haemoglobin levels, as well as the "type, dose, and duration" of deferasirox iron "chelation therapy".

Material and Methods

The research has been carried out at the Thalassemia Research Medical Center of the Ibn-Atheer Teaching Hospital in Mosul city, Iraq. Patients with thalassemia were all registered at this centre in order to benefit from the services provided there as well as the treatment administered which is almost free by the Iraqi government. These patients have received a blood transfusion as well as an oral iron chelator, deferasirox. They were chosen using a straightforward random selection procedure, which was carried out with the assistance of computerized tables and software. A total of 60 patients with thalassemia were randomly selected. Participants in the study were subjects with transfused "dependent beta-thalassemia major" who had been undergoing chelation for at least 2 years and were between the ages of 12 and 40 years old. They were evaluated for their symptoms as part of the case group. They were also received frequent blood transfusions of packed red cells at intervals of 15–30 days in order to maintain haemoglobin concentrations above 9 g/dl in all of them. The participants' eyes were examined by an ophthalmologist with the use of a slit lamp and an ophthalmoscope.

All thalassemic patients had their serum ferritin levels measured at regular intervals in their blood during the course of their treatment. Before each transfusion, the haemoglobin level was checked, and the results were entered into their medical records as necessary. The frequency and duration of their transfusions, as well as the serum ferritin level and pretransfusion haemoglobin levels, as well as the type of chelation therapy they were receiving, as well as the length of time and daily dose they received, were all determined from their records.

Another 60 apparently healthy control individuals were enrolled from the Ibn Atheer Teaching Hospital's staff in order to compare the findings with those of normal healthy subjects. They were all of the same age and gender as the participants in the research with no previous histories of iron deficiency or any other blood problems among them in the control group.

Following the Declaration of Helsinki procedure, written consent were collected from all participant before taking part in the study. [9]The nature of the study was explained in detail to all participants following the rules of ethics outlined in the Declaration of Helsinki procedure. Each patient was subjected to a thorough examination of his or her vision. To determine visual acuity and refractive error, several tests were performed during the eye examination. These tests included "tear break-up time (TBUT)" tests and color vision tests[10]. To determine the degree of refractive error present, the auto refractometer was utilized[11]. Acuity was assessed monocularly at a distance of 6 m using a bright 100 cm^2 light source and a tumbling E chart with retro illumination at 100 cm^2 using a bright 100 cm^2 light source[12]. In this study, the researchers calculated both the uncorrected and the best-corrected visual acuities. To evaluate each eye, the following procedures were performed: slit lamp biomicroscopy, ophthalmoscopy, and intraocular pressure measurement with a tonometer. It was necessary to do the TBUT test on an individual in order to identify whether or not they had dry eye syndrome[13,14]. The BUT was examined under "a slit lamp microscope" equipped with a "cobalt blue filter", and the procedure was carried out without the use of topical anaesthesia or sedation[15]. "Fluorescein solutions" were injected into the conjunctival sacs of the subjects with the goal of diagnosing their medical status[16]. To ensure that the fluorescein was dispersed uniformly throughout their bodies, the subjects were asked to blink repeatedly and continuously for 3-5 seconds after the fluorescein was administered. According to the findings of this study, the amount of time that passed between the last "full blink" and the "first tear film" breakage was measured. In this particular instance, TBUT less than 10 seconds was regarded to be dry eye, see the used instrument in Table 1.

Table 1. Instruments used to conduct the research.

Instrument	manufacturer	Origin
Autorefractometer	Topcon KM 8900	Japan
Biomicroscopy	BQ 900: HaagStreit	Switzerland
Ophthalmoscopy	Heine Beta 200;	Germany
Tonometer	Goldenman	United kingdom

Patient capacities and their capacity to depend on the information gained through VF testing are directly related to one another[17]. In order to acquire the required results, it was essential to repeat the test in individuals who had considerable fixation loss (more than 30%), major "false positive" (>39%), and significant "false negative" (>50%) during the first attempt (>36%).

The global hemifield test, the grayscale test, as well as the total and pattern deviations of each individual patient are all taken into consideration when interpreting VF findings. In order to quantify VF loss numerically, it was determined that global indices would be used.

Patients with thalassemia have been found to have statistically significant ocular abnormalities concerning the number of blood transfusions they have received, the serum ferritin level, as well as the type, dosage, and duration of chelation treatment they have received. It was determined which group had a higher prevalence of visual alterations in this study by comparing the prevalence of ocular changes in thalassemic patients to the prevalence of changes in healthy controls.

Results

The participants in this trial were sixty thalassemic patients who were being treated with deferasirox. In this investigation, only the information from the "right eye" was used, and the data from the left eye was discarded since the "contrast thresholds" in the right and left eyes were associated ("Pearson correlation coefficient"; r=0.786, P=0.000). The control group comprised of 60 healthy adults with a mean age of 24.70 3.46 years and a standard deviation of 3.46 years. Based on the group they were assigned to, the individuals ranged in age from 20 to 30 years old, depending on their gender. The variation of the two groups was not significant in terms of gender or age (P=0.731 for gender and P=0.524 for age).

It was determined that the ''interquartile range" (IQR) and the median and of both cylindrical and "spherical refractive errors" in the thalassemic patient and control groups were the same (Table 2). To determine whether the median values of the study groups differed from one another, the median test was performed on the data. The "spherical refractive errors" of the two groups differed significantly (P=0.005), but the cylindrical refractive errors of these groups did not differ significantly (P=0.565). The patient group on deferasirox did not have any symptoms and had no abnormalities in their ocular system when they were examined by an ophthalmologist. They had no pathological or structural abnormalities in their ocular system when they were examined by an opthalmologist. The mean and standard deviation (mean SD) for "best-corrected visual acuity" were 1 minute of arc in all tested subjects. The following findings appeared in thalassemic patients are shown in Table 3. A comparison of all participants' mean standard deviation (mean SD) contrast threshold is shown in Table 4 and Figure 1-a and b. Three distinct spatial frequencies were investigated in order to identify the contrast threshold for each (1, 5, and 15 cpd). An "ANOVA test" found that there was a statistically significant difference between the contrast thresholds of patients in the deferasirox and control groups for all of the "special frequencies" tested. Even though the difference between the deferasirox and control groups was not significant for 1 and 15 cpd, the deferasirox group had a greater contrast threshold than the control group for all special frequencies. It was discovered that the contrast thresholds in the group that utilized deferasirox were greater at all special frequencies when compared to healthy people, but that the difference was not statistically significant.

It has been shown that the contrast threshold is correlated with the level of ferritin, the dose of iron chelators, and the time duration blood transfusion will last, as determined by the Pearson correlation coefficient (see Table 5).

Table 2. Cylindrical and spherical "refractive errors" in cases and controls.

	Spherical errors	Cylindrical errors
	Median(IQR **=Q1-Q3)	Median(IQR=Q1-Q3)
Deferasirox Cases	0.00(0.01-0.25)	-0.25(-0.40-0.01)
Control subjects	0.00(0.01-0.25)	-0.25(-0.40-0.01)
P-value	0.004	0.465
*Median test used for analysis.**IQR=(Q1-Q3)=Interquartile range.		

Table 3. Characteristics of thalassemic patients who received iron chelator deferasirox.

	Repeated blood transfusion (Year)	Serum ferritin level (mg/L)	Iron Chelator dose (mg/kg/day)
Deferasirox Cases	20.3.4±3.20 (15-28)	3123±1765(500-6000)	37.90±8.56(17-71)

Table 4. The mean "contrast threshold" of thalassemic patients and healthy or control subjects were determined.

Special Frequencies	Study Group	Contrast threshold mean±SD [Range]	P-value
1 cpd	Deferasirox	1.87±0.63[0.51-3.44]	0.009
	Control	1.33±0.58[0.51-2.79]	
5 cpd	Deferasirox	1.46±0.81[0.50-2.95]	0.022
	Control	0.95±0.68[0.51-2.54	
15 cpd	Deferasirox	2.96±1.68[0.51-6.88]	0.135
	Control	2.24±1.23[0.51-5.98]	

Figure 1. A representative image for ocular examination of thalassemic patients A. Ocular changes in thalassemic patients on deferasirox B. Ocular changes in thalassemic patients on deferasirox

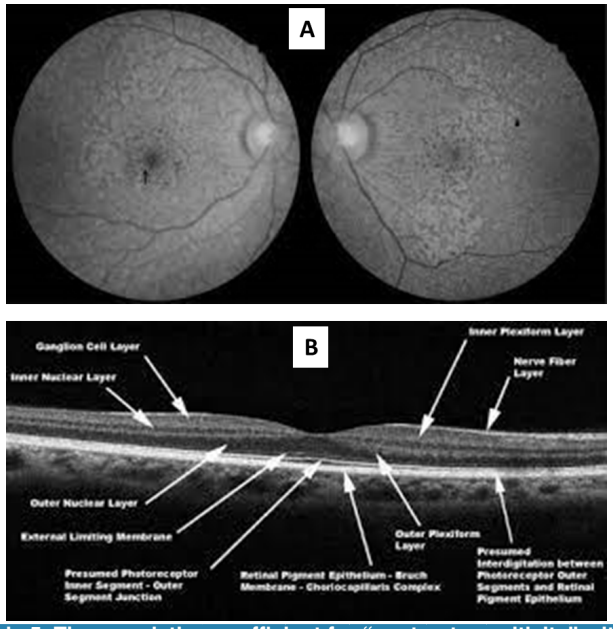

Table 5. The correlation coefficient for "contrast sensitivity" with "serum ferritin level", deferasirox dose and duration of regular blood transfusion.

	Serum ferritin level		Duration of blood transfusion		Deferasirox dose	
Contrast Threshold (In Deferasirox users)	P value	r	P value	r	P value	r
1 cpd	0.94	0.004	0.03	-0.39	0.47	0.136
4 cpd	0.06	0.346	0.18	0.246	0.19	0.246
14 cpd	0.22	0.230	0.90	0.023	0.42	0.150

Discussion

When patients have hematologic problems that necessitate frequent blood transfusions in order to prevent hemosiderosis, iron-chelating medications are utilized to treat their iron overload[19]. Using this study's findings, it was discovered that the ''contrast threshold'' in patients with significant thalassemia who received deferasirox was higher than the contrast threshold in patients who received deferasirox and also in healthy individuals across all spatial frequencies[20], but that the difference between the two groups was not statistically significant[21]. Although thalassemic individuals had no trouble with basic "visual acuity tests" such as the "Snellen chart", they did have difficulty with several other examinations[20,22]. No correlation was detected between "contrast sensitivity" levels and transfusion duration, mean "serum ferritin concentration", or the dose of "chelation therapy" utilized in the trial, as previously reported.

Previous research has also approved parallel outcomes; for example, Ghazanfari et al discovered that the contrast detectability serves in all "beta-thalassemic patients" with "normal visual acuity" was considerably drop than in control apparently healthy individuals for all spatial frequencies evaluated in comparison to the normal control group, as previously reported[20].

According to the findings of the study, individuals with substantial thalassemia had lower contrast sensitivity values than normal participants when the results were compared to the results of the study for normal participants at the same frequencies.

Ocular problems have been reported in people who have had significant thalassemia in the past, but these have not been confirmed. Among these are "lens opacity", "macular degeneration", "retinal vascular alterations", and degeneration of the "retinal pigment epithelium"[23].

Although it is not entirely clear what caused the ocular anomalies, some experts deem that iron overload, rather than chelation therapy, was the primary cause, while subsequent deem that chelator administration, particularly deferasirox, has toxic consequences and can harm the eye in a variety of ways. Aside from that, unstable blood haemoglobin levels that persist despite regular blood transfusions may result in persistent retinal hypoxia and impairment of the function of the retinal cells, as well as other complications.

Those with abnormal eye predicaments or systemic disorders such as diabetes, which can have a negative impact on the visual system, were not included in the current study[24]. Because of a disruption in the blood-retinal barrier in diabetic patients, it is hypothesized that deferasirox is able to penetrate the retina more readily than in usual patients, and as a result, subsequently cause more harmful effects than in normal patients[25]. As an alternative, we exclude thalassemic patients who have severe refractive defects, particularly myopia, from consideration (high prescription). The Bruch layer appears to have been altered in these patients, which suggests that iron precipitation would be loftier in these patients, and as a result, more adverse effects would be expected. Note that, as in previous studies, our selected sample of thalassemic patients had significantly lower contrast detectability than healthy subjects, even though they did not have any obvious pathological or structural changes in their ocular system (as opposed to healthy subjects), particularly in those who received oral deferasirox (as opposed to those who did not). This was especially true in the case of those who received deferasirox iron chelation therapy. We found a non-noticeable ocular defect in our sample of patients, but earlier research has revealed that electrodiagnostic testing, fluorescein angiography, and other tests such as perimetry may reveal certain abnormalities.

The researchers found no problems when they examined their patients under a slit lamp, but when they used fluorescein angiography they discovered angioid streaks and RPE degeneration in 11% of those who took part in the study[26]. It was also discovered that those who had the ocular disease as indicated by fluorescein angiography experienced greater contrast sensitivity loss when compared to those who did not have any issues with the procedure during the investigation[27].

We discovered that there was a statistically significant difference in contrast sensitivity between individuals who were thalassemic and who took iron chelator medicines, according to the results of our investigation. It was discovered in the current investigation that the contrast sensitivity of the deferasirox group was significantly lower than that of the non-treated group. Because those who used deferasirox had a greater reduction in contrast detectability, they may be able to detect some anomalies in more extensive tests.

In order to determine the correlation between the dose of chelator drugs used and the average serum ferritin concentration as well as the intervals of blood transfusions given to patients with ocular complications, several studies have been conducted.

Its findings were similar to those of Ghazanfari *et al.* 2019[20], who discovered that there was no relationship between the time of a blood transfusion, the dose of chelator used, and serum ferritin levels or contrast sensitivity[20,21]. In their conclusion, they state that persistent retinal hypoxia is the most likely cause of contrast sensitivity loss, with other effects for example the "duration of blood transfusion", duration of iron chelator medication, and "serum ferritin levels" playing a less significant role in this process. When we looked at another sample of "thalassemic patients", we discovered a statistically significant positive relationship between the "prevalence of ocular abnormalities" and the number of "blood transfusions", but not a relationship between the "mean serum ferritin level" and the dose of chelator drugs, as previously reported. This results in difficulties in making precise comparisons between research because of the variation of the age range of the studied group in different studies.

In contrast, the findings of our investigation demonstrated that there was no association between the doses of chelator drugs and the loss of contrast sensitivity, despite various assertions regarding the usefulness of deferasirox dosage on visual function. We can't rule out the possibility that the modest dose of a chelator that our patients received was the

source of their symptoms. A study found that doses less than 50 mg/kg/day of deferasirox were less likely than higher doses to cause structural eye abnormalities, but they were more likely to cause hearing impairment. According to our data, chelators were administered at levels less than 50mg/kg per day to 90 per cent of our study participants.

Our ability to analyze the complete influence of deferasirox on patients' contrast sensitivity function was limited by the small number of cases studied and the short amount of time during which they were treated[28-30]. Furthermore, we do not examine or accept patients who have dry eyes, and we do not provide treatment to these patients. It was determined that it was preferable to exclude participants who had dry eyes from the study based on the findings regarding the degree of correlation between thalassemia and dry eye, which could have some implications for the outcomes of the contrast sensitivity test. Participants who had dry eyes were excluded because of the findings regarding the degree of correlation between thalassemia and dry eye.

Conclusion

Several ophthalmic illnesses, as we all know, can be detected early on through the use of "contrast sensitivity tests", which can detect visual abnormalities before the deterioration of "visual acuity" becomes apparent. It is recommended therefore that thalassemic patients undergo regular eye examinations and that if they experience any reduction in contrast sensitivity after being diagnosed, they are referred to a doctor for evaluation to determine whether or not their treatment regimen with an iron chelator, deferasirox should be changed in order to avoid the development of further complications

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Conflict of Interest
There is no conflict of interest.

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