

Evaluation of Retinal Changes in preclinical chloroquine maculopathy using spectral domain optical coherence tomography

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الهدف من الدراسة :

تقييم التغيرات الحاصلة في شبكية العين باستخدام التصوير المقطعي الضوئي لغرض الكشف المبكر للاعتلال الشائبة الصفراء للمرضى العراقيين الذين يعانون من داء المفاصل الرثوي والذين تمت معالجتهم باستخدام عقار الكلوروكوين .

الاساليب:

تم ادراج تسعون مريض في هذه الدراسة حيث قسم المشاركون الى مجموعتين . المجموعة الاولى وشملت اربعون مريض يعانون من التهاب المفاصل الرثوي تمت معالجتهم باستخدام الكلوروكوين لفترة زمنية تجاوزت العامين وكان جميع المرضى لا توجد عليهم العلامات السريرية للاعتلال الشائبة الصفراء الناجم من الكلوروكوين. المجموعة الثانية تكونت من خمسون امراه غير مصابات باي مرض . تم تقييم كلتا المجموعتين باستخدام التصوير المقطعي الضوئي.

النتائج :

معدل السمك المركزي للشائبة الصفراء كان اقل في مجموعة الكلوروكوين (228.94 ± 4.31 مايكرون) مقارنة بالمجموعة الاخرى (255.12 ± 11.54) و كان الفرق معتد به احصائيا

الاستنتاج :

سمية الكلوروكوين ممكن ان تنتج تغيرات في سمك الشائبة الصفراء قبل ظهور أي اعراض سريره لها . انه بالامكان الكشف عن هذه التغيرات باستخدام التصوير الضوئي المقطعي.

Abstract:

Purpose: evaluation of retinal changes using spectral-domain optical coherence tomography (SD-OCT) in early detection of Chloroquine maculopathy in Iraqi patients with rheumatoid arthritis (RA).

Methods: ninty six patients were included in this study .They were divided into two groups . First group compose of (46) patients with RA(rheumatoid arthritis) who received chloroquine therapy for more than two years. All patients had no clinical feature of Chloroquine retinopathy. Second group (control group)were (50)normal female. They were evaluated using SD-OCT.

Results:The mean central foveal thickness(CFT) was less in the Chloroquine group ($228.94 \mu\text{m} \pm 4.71$) compare to normal controls ($255.12 \mu\text{m} \pm 11.54$), which was statistically significant (p value 0.001). The mean parafoveal thickness was thinner in the Chloroquine group than other group in superior,inferior and temporal quadrants .

Conclusions: In the preclinical stage, chloroquine toxicity might result in early thinning involving mainly central fovea and parafoveal zone ,this changes can be detected by SD-OCT

Introduction:

From the time of their introduction the anti-malarial drugs, chloroquine and hydroxychloroquine, are widely known and used all over the world¹. They are frequently used as disease-modifying antirheumatic drugs for autoimmune disorders like rheumatoid arthritis, scleroderma², systemic lupus erythematosus³.

These drugs were associated with the potential risk of developing retinopathy as a serious ocular complication with permanent loss of vision. Both of these agents cause retinopathy but differ in therapeutic dose ranges with hydroxychloroquine considered a safer option^{4,5}.

In addition to retinal toxicity, antimalarial drugs may have other toxic effect at eye level like spiral pattern of epithelial keratopathy, subcapsular cataract and damage with subsequent atrophy to the optic nerve⁵.

The retinal toxicity of chloroquine may be the result of toxic effects of metabolic by-products from photo pigment recycling. Lipofuscin is an accumulation of breakdown products of visual pigments within the RPE. Lipofuscin's main component is *N*-retinylidene-*N*-retinylethanolamine

(A2E) with lesser amounts of isoA2E, all-transretinal dimephosphatidylethanolamine, and alltrans-retinal dimer-E. A2E is photooxidized to peroxy-A2E, furano-A2E, and epoxides⁶.

These endoperoxides are potentially cytotoxic and may cause RPE damage and atrophy.

Other explanation to the toxic effect of these agents on the retina appears as a consequent to their affinity to bind melanin containing layers in the eye like the retinal pigment epithelium⁷.

The clinical feature of retinal toxicity by antimalarial drugs have been well elucidated; in early stages, changes are

not significant but it is possible to observe diminished foveolar brightness or subtle pigmentary changes in both eyes⁸. In this stage, the patient either asymptomatic or presented only with limited difficulties in reading. Scotomas and more difficulties to read start to appear with the progression of the disease⁹.

In the ophthalmologic examination the characteristic "bull's-eye" image can be seen, which is caused by depigmentation of the retinal pigment epithelium in the macula with a small central island spared¹⁰. If exposure to the drug continues, there would be retinal pigment epithelium atrophy initially in the macular region that can progress outwards to cause retinal atrophy. This will produce a decrease in visual acuity, as well as in color and night vision. In advanced stages, funduscopic changes can resemble to those of retinitis pigmentosa with diffuse retinal changes and vascular thinning¹¹.

The development of toxic retinopathy is principally related to the dose of antimalarial agents and perhaps it could be reversible if we stop the drug at the preclinical stage¹².

The patients, in early stage of retinopathy might be asymptomatic, and the fundus may remain normal for a while before any signs of maculopathy appear; hence, screening for early detection in the premaculopathy stage is necessary¹³.

Although chloroquine has been widely replaced by hydroxychloroquine in treatment of rheumatoid arthritis due to its wider safety margin, it is still in use in our area for socioeconomic reasons. This made the screening and early detection of retinal toxicity an important issue.

The screening for retinopathy in patients receiving chloroquine involves:

visual acuity assessment, examination of fundus with slitlamp biomicroscope. Other testing methods which is used

infrequently include fundus photography, and fluorescein angiography¹⁴.

The problem with all mentioned tests that it is not possible to detect toxic retinopathy at preclinical level¹⁵.

For early detection of the anatomical and functional abnormality affecting the retina, it has been recommended to use more sophisticated investigation, fundus autofluorescence, multifocal ERG and spectral-domain optical coherence tomography (SD-OCT) with high resolution may prove to be valuable tools in early detection of chloroquine toxicity^{15,16}.

SD-OCT is an objective, quick, and reproducible technique to examine the anatomy of the retina and optic nerve, which makes it a useful screening tool. Recent studies have shown that changes in retinal thickness and loss of outer retinal layers can be detected by SD-OCT in patients with early chloroquine toxicity, even in areas that appeared normal on fundoscopy and perimetry¹⁷. Detection of these changes in preclinical stages can be invaluable in screening for chloroquine maculopathy.

In this study, we compared macular thickness using SD-OCT in patients having rheumatoid arthritis and receiving chloroquine therapy for more than two years to a group of normal individuals to identify whether SD-OCT could be a possible tool for detecting preclinical macular toxicity in this group of patients.

Materials and Methods:

This case control study was performed at Diwaniya teaching hospital for evaluation of structural changes in the retina of Iraqi patients taking chloroquine.

Forty six female patients who are complaining from rheumatoid arthritis whose age ranging from (35 -67) years were compared with fifty normal female of the same age group.

The first group was receiving chloroquine therapy for period ranging

from (2-6) years. All of them have no any clinical feature of chloroquine toxic maculopathy at time of study. The second group was completely normal control with no history of systemic disease. Participants were recruited from rheumatology and ophthalmology units at Diwaniya teaching hospital.

The study followed the principle of Helsinki declaration and ethical approval was taken from ophthalmology department committee.

Patient was excluded from the study if they have any of the following disorders: glaucoma, previous retinal surgery, diabetic retinopathy, chorioretinal scar or any macular disease.

After taking an informed consent from all the participants, a thorough history including age, duration of illness, duration of treatment and calculation of the cumulative dose till time of study, presence of visual complaints like scotoma or vision distortion.

At the ophthalmology unit, complete examination was done including: assessment of best corrected visual acuity using illiterate E-chart, pupillary reaction, slit lamp examination with evaluation of posterior pole using 90 diopter fundus condensing lens, IOP measurement using air puff tonometer, visual field assessment using octopus field analyzer and assessment of color vision using Ishihara pseudoisochromatic plate.

For structural evaluation of retina spectral domain optical coherence tomography was done for all the participants, machine used in this study was RTVue (Optovue, USA).

Steps of examination was as follows: patient sit in a comfortable way, he put his chin on chin rest with his forehead against forehead strap. patient was asked to fixate on target light throughout the examination.

Central foveal thickness, parafoveal thickness (in four quadrants superior

,inferior,temporal,nasal) and integrity of inner segment –outer segment of photoreceptor junctions were assessed. Scan method used was electronic macular map 5 mm(EMM5) which is a 5 × 5 mm square grid centered on fixation; the grid spacing, which is 0.25 mm in the inner 3 × 3 mm area and 0.5 mm in the outer area. Average of 4 scan was taken per eye.

Statistical analysis

Data were analyzed using statistical package for social sciences (SPSS version 22). Numeric variables were expressed as mean, standard deviation (SD) and range whereas categorical variables were expressed as number and percentage. Independent samples student t-test was used to compare mean difference between groups

Table 1: Demographic data of both groups.

variable	chloroquine group		2 nd group(control)		P value*
	Mean+_SD	range	Mean+_SD	range	
Age in year	54.37 ±5.49	35-65	51.67 ±7.19	39-67	0.87
Duration of illness(years)	5.3±2.2	2.1-7.4	-	-	-
Duration of chloroquine treatment(years)	3.4±2.3	2.3-5.7	--	--	--

*independent sample t-test

Finding of OCT (optical coherence tomography):

Macular finding on OCT shown in table2 .There was statistically significant thinning involving central foveal thickness(CFT) in chloroquine group compare to control group(CFT was 228.94±4.77 micron in chloroquine group vs.255.12±11.54 micron in control group ,p value <0.001).

In parafoveal region ,there was statistically significant thinning affecting

Table2 SD-OCT parameter in chloroquine and control group

Variable	Cloroquine group (n = 40)		Control (n =50)		P *
	Mean ± SD	Range	Mean ± SD	Range	

while Pearson correlation was used to evaluate correlation between any two numeric variables. P-value was considered significant when it was equal or less than 0.05.

Results:

Total number of 96 participants were recruited in this study .They were divided in two group. First group (chloroquine group) compose of 46 patients with rheumatoid arthritis while second group were 50 normal control. All the participants were female with age range from (35 -67) years. Those patients receiving chloroquine on fixed dose of 200mg twice daily with duration ranging from 2-6 years. All patients had normal ophthalmic examination. Demographic data of participants shown in table 1.

superior, inferior and temporal quadrants in chloroquine group compare to controls(superior 313.74±8.37 in chloroquine group vs 321.05±11.05 in controls ;p value 0.003,inferior 313.13±9.95 in chloroquine group vs 326.16±9.74 in controls ;p value <0.001 and temporal quadrant 307.35±9.81 in group 1 vs 317.37±12.81 in controls, p value <0.001)

Central Foveal Thickness	228.94 ±4.77	219 -238	255.12 ±11.54	236 -286	<0.001
Superior quadrant**	313.74 ±8.37	302 -329	321.05 ±11.05	294 -346	0.003
Nasal quadrant**	312.48 ±13.54	285 -349	315.49 ±13.13	294 -348	0.341
Inferior quadrant**	313.13 ±9.59	301-338	326.16 ±9.74	304 -341	<0.001
Temporal quadrant**	307.35 ±9.81	289 -324	317.37 ±12.81	300 -348	<0.001

*Independent samples t-test

**parafoveal zone quadrants

There was significant correlation between the duration of treatment and retinal thickness when analyzed by Pearson correlation test.

Table 2: Correlations with duration of treatment

Pearson correlation	CFT	Parfoveal quadrant			
		S	N	I	T
r	-0.747	0.274	-0.238	-0.159	-0.104
P	<0.001	0.136	0.198	0.393	0.578

r: correlation coefficient; P: P-value:

Discussion:

Screening for chloroquine retinopathy especially in its early stage still a challenging issue since in the preretinopathy stage macular changes as well as functional tests e.g central field test might resemble that of other age related changes¹⁸.

From another aspect, chloroquine maculopathy consider as irreversible condition and all the retinal changes and visual functions deterioration might continue even following cession of this therapy¹¹.

These facts necessitate the need for early detection of maculopathy at preclinical level.

There is numerous tests used for screening of chloroquine toxicity on the retina but the sensitivity and specificity of each test is still being debated.

Spectral domain optical coherence tomography consider as essential investigation for detection of toxic maculopathy as several studies conducted on patients taking chloroquine and hydroxychloroquine reported retinal

thinning and loss in outer layers of retina with early retinal toxicity^{15,16}.

Passadhika et al¹⁴ had report retinal thinning affecting mainly parafoveal region on SD-OCT in those taking hydroxychloroquine, however this study was done on clinically symptomatic patients.

In our study we found patients receiving chloroquine for treatment of rheumatoid arthritis , even though had no clinical feature of retinal toxicity, but SD-OCT revealed their central foveal thickness and parafoveal thikness in four quadrants were less compare to normal control.

This indicate OCT can detect retinal toxicity at early stage even when other tests still normal.

Our results agree with that of Riham et al who found decrease in central foveal thickness in asymptomatic patients taking chloroquine treatment¹⁸.

This result indicate early affection of fovea by the chloroquine which is due to narrow safety margin of this drug. The extent of damage in the macular area is thought to be related to ganglion cell distribution, as found by primate studies

¹⁹. Additionally, the binding of chloroquine to melanin pigment in the RPE and presence of avascular zone at the center of the fovea has been suggested as a possible explanation for the distribution of damage.

American academy of ophthalmology in 2011 reviewed the risk of chloroquine/hydroxychloroquine maculopathy and concluded that high risk group had duration of treatment more than five years, cumulative dose exceed (460 gram) of chloroquine and (1000 gram) of hydroxychloroquine, daily dose more than (3mg per kg daily) for chloroquine and more than (6.5 mg per kg daily) for hydroxychloroquine, elderly, kidney and liver dysfunctions.

However in our study we found structural retinal changes in SD-OCT appear in less than expected time for the toxicity (about three years).

In our study we exclude patients with hepatic and renal impairment as these conditions increase risk of toxicity since it affect metabolism of these drugs.

There are several limitation in this study eg the relative small number of participants and also we did not involve functional test like multifocal ERG. This need further study in the future also to find the correlation between body weight and structural retinal changes.

In conclusion, there is retinal thinning involving both central foveal and parafoveal region in patients taking chloroquine therapy compare to normal control when examined by SD-OCT.

SD-OCT is valuable in demonstration of early retinal changes in patients on chloroquine treatment. Our study suggest OCT should be part of routine screening for chloroquine maculopathy even when all other test are normal.

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