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Comparative study between visual evoked potential and visual acuity, field of vision, and fundus examination as screening tool for early diagnosis of hydroxychloroquine and chloroquine retinal toxicity in rheumatic patients

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Comparative study between visual evoked potential and visual acuity, field of vision, and fundus examination as screening tool for early diagnosis of hydroxychloroquine and chloroquine retinal toxicity in rheumatic patients

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Abstract

Objectives

The current study was conducted to compare between the conventional eye examination methods named as visual acuity, fundus examination, and field of vision evaluation in one hand and electrophysiologic methods of eye examination as visual evoked potential eye study in the other hand in detecting antimalarial medications toxicity on the eye macula in rheumatic patients.

Materials and methods

Fifty rheumatic patients group and fifty healthy control group age and sex matched were studied. Patients receiving anti-malarial medications for more than 6 months with cumulative dosage of at least 200 grams were included. All patients and control were subjected to full history and ocular examinations including visual acuity testing, fundus examination, visual field examination, and electrophysiological examinations (visual evoked potential) VEP.

Results

There was a statistical significant difference between percentage of patients and control group who having abnormal field of vision with $P < 0.01$, however there was no statistical significant difference between percentage of patients having abnormal visual acuity and control group with ($P = 0.06$). There were statistical significant difference between percentage of patients and control group who having delayed P100 latency, low amplitude of P100 wave, abnormal (IOD) of P100 latency and amplitude with ($P < 0.001$). P100 latency was superior in sensitivity and specificity (57% & 98%) not only on field of vision but also superior on other VEP parameters, and both P100 latency and amplitude increased the sensitivity of VEP test to 62% and specificity to 100%. P100 latency of VEP is significantly correlated with duration of treatment with antimalarial drugs ($r = 0.529 - P < 0.001$ & $r = 0.285 - P = 0.04$). However, there is no significant correlation between duration of treatment and other VEP parameters.

Conclusion

We conclude that P100 latency of VEP can be useful parameter to detect CQ/HCQ retinal toxicity as it was superior in sensitivity and specificity and is significantly correlated to duration of treatment with antimalarial drugs, however, both field of vision examination and P100 amplitude parameters are inferior to P 100 latency in detecting macular changes.

Keywords: visual evoked potential, field of vision, hydroxychloroquine and chloroquine, retinal toxicity

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Body

Chloroquine (CQ) and hydroxychloroquine (HCQ) are the most common antimalarials used for the treatment of autoimmune and connective tissue diseases, including systemic lupus erythematosus, rheumatoid arthritis, psoriatic arthritis, palindromic rheumatism, dermatomyositis, Sjögren's syndrome, and juvenile chronic arthritis [1].

Although long-term use of both has various adverse effects such as gastrointestinal upset, skin rash, headache, and eye abnormality, a major concern is their effect on different ocular structures, including ciliary body involvement, crystalline lens opacity, as well as retinopathy and keratopathy [2]. Moreover, major effects on the retina causing permanent visual loss have been reported. Therefore, early detection of ocular adverse effects owing to HCQ is necessary to prevent consequent serious ocular problems [3].

Its toxic effects on the retina are seen in the macula. Although early toxicity may be asymptomatic, patients with a more advanced stage of toxicity may complain of color vision changes or paracentral scotomas. As retinal toxicity is usually irreversible, early detection of retinal toxicity and cessation of the offending agent is the best treatment. A high-risk patient is one who receives greater than 6.5 mg/kg/day for more than 5 years with coexisting retinal disease, liver or kidney disease, age greater than 60 years old, and high-fat level (unless the dosage is appropriately reduced for ideal body weight). High-risk patients have a 5% chance of developing toxic retinopathy [4].

HCQ continues to be a valuable drug in treating rheumatic diseases, but clinicians need to be aware of the associated risks and to have arrangements in place that would enable early detection of toxicity [5].

Basic ocular examination is recommended before starting treatment, and annual examination, including visual acuity measurement, funduscopy, and visual field (VF) examination, should be done [1].

Regarding VF examination Humfrey field area 24–2 test used as a type of central VF examination, the sampling of the central VF area may be under-powered. There is a wide agreement between researchers and clinicians that the low spatial resolution of this program in the central macular representation might be a major factor of the underestimation of functional deterioration in early detection of central retinopathy with this test [6].

Therefore, the central VF area can be selectively and more accurately tested using the Humfrey field area 10–2 test which employs a test-point grid of higher spatial resolution for the assessment of the central 10° VF area. It has 68 test-point locations evenly distributed with 2° separation in the central 10° [7].

The fundus examination (ophthalmoscopy) can remain completely normal even after the central scotoma development.

The earliest signs of toxicity are the fine pigment stippling of the macula, some irregular pigmentation changes, and loss of the foveal light reflex, sometimes referred to as maculopathy [8].

Visual evoked potentials (VEP) are used to assess the visual conduction pathways through the optic nerves and brain. To measure VEP, VFs are stimulated, usually with a checkerboard visual stimulus, and the evoked response is recorded using surface recording electrodes over the occipital lobe. Three standard stimulus protocols are defined for recording VEP where the pattern-reversal VEP is the preferred stimulus for most purposes because it has relatively low variability of waveform and peak latency both within a subject and over the normal population. A normal VEP response to a pattern-reversal stimulus is a positive peak that occurs at a mean latency of 100 ms. There are three separate phases in the VEP waveform: an initial negative deflection (N75), a prominent positive deflection (P100), and a later negative deflection (N145). The peak latency and peak-to-peak amplitudes of these waves are measured [9].

Some authors reported that a P100 latency of VEP and photo stress recovery time (PSRT) tests were the best predictors in early stages of maculopathy, with the P100 latency of VEP being the best predictor in patients without ocular symptoms and fundoscopic lesions [10]. Others have suggested the evaluation of central VF as the best test for the early diagnosis of HCQ toxicity [6].

It has been observed that HCQ causes perifoveal changes in retinal pigmented epithelium layer, which induces abnormal readings in central field of vision and VEP [11].

Therefore, in our study, we compared the sensitivity and specificity between VEP as a traditional test, and as it can assess visual function objectively, against the other suggested subjective tests such as visual acuity, a field of vision, and fundus examination, so its results can be more reliable.

PATIENTS AND METHODS

The study protocol was approved by the Ethics Committee of GOTH. This cross-sectional study included 50 healthy control group and 50 rheumatic patients receiving antimalarial medications for more than 6 months with a cumulative dosage of at least 200 g based on the patient's daily dose and duration. All patients and control were subjected to full history and ocular examinations including visual acuity testing, fundus examination, VF examination, and electrophysiological examinations including VEP.

Inclusion criteria

Patients who are treated for various rheumatologic diseases by CQ/HCQ medications as 200–400 mg per day with a cumulative dose of at least 200 g with the following inclusion criteria were included:

- (1) Patients should be treated for more than 6 months
- (2) Patients who have or not have visual symptoms
- (3) Patients aged 20–50 years old.

Exclusion criteria

The exclusion criteria were as follows:

- (1) History, physical examination, and laboratory investigations were conducted to exclude other predisposing factors for retinopathy such as diabetes mellitus
- (2) Patients who are older than 50 years are excluded
- (3) Local eye diseases such as very high myopia or cataract are excluded.

Ophthalmic examination in the form of visual acuity testing, fundus examination, and field of vision examination was done for every patient at the beginning of the study by an ophthalmologist.

All the following tests were performed for all patients and controls:

- (1) Best-corrected visual acuity using Tumbling E optotype visual acuity testing on decimal projector chart
- (2) Complete anterior segment examination using slit-lamp Biomicroscopy
- (3) Complete posterior segment examination using indirect ophthalmoscopy.
- (4) Intraocular pressure measurement
- (5) Complete ocular mobility examination
- (6) VF testing and analysis using Humphrey visual field (VHF) analyzer. A Carl Zeiss Humphrey 750 Field Analyzer using the Sita fast technique was performed in a separate dark quiet room. The VHF area of 10–2 was performed for testing the central field of vision SPSS statistical program version 21 ‘Microsoft excel XP version’ (USA)
- (7) 2-10 threshold VF testing assesses 68 points. These points are all 2° apart, just 1° from either side of the horizontal and vertical meridians. As a result of this greater sensitivity, many paracentral scotomas are only detected with 10–2 testing
- (8) VEP electrophysiological test using checkerboard visual stimulus is done for every patient.

VEP was recorded with a PC based, 2 channel, RMS EMG EP mark II machine and standard silver chloride disc electrodes. A one channel montage was used for recording the VEP. The scalp electrodes were placed relative to bony landmarks, in proportion to the size of the head, according to the International 10/20 system. The active electrode was placed at Oz which is the highest point of the occiput, lies over the visual cortex. The reference and ground electrodes were put at Fz and Cz (vertex), respectively. The recording was done in a dark room with quiet surroundings. Visual stimulation was done with a checkerboard pattern generated on the monitor using the software installed, which consisted of black and white checks whose phase was reversed (black to white and white to black) at a fixed rate of two reversals per second. The subject was seated at a fixed distance of 75 cm from the screen and was asked to fixate at the center of the screen. Monocular stimulation was given to both the eyes separately. A sweep length of 250 ms was done,

and more than 100 responses were averaged. An amplification range of 20 000–1 00 000 was used. To ensure reproducibility, the waveform was recorded twice. The electrode impedance was kept less than 5 kΩ. The VEP parameters recorded were latencies to N75, P100, and N145 waves; peak-to-peak amplitude of P100 wave; and intraocular p100 differential latencies and amplitudes [12].

Statistical analysis

All tabulated data were expressed as mean ± SD. Comparisons between patients and control groups was done by using the Student *t* test. For all statistical tests, the significance was tested using the correlation coefficient (*r*) test in which significance is defined as level of probability ‘*P*’ value of less than 0.05. Computations were done using an SPSS statistical program version 21. Graphs were assessed using Microsoft excel XP version.

RESULTS

We studied 50 healthy control group and 50 rheumatic patients (45 complaining of rheumatoid arthritis and five complaining of SLE) receiving antimalarial medications for more than 6 months, with a mean age of 38.9 ± 9.7 and 40.8 ± 9.9 years, respectively.

The mean cumulative dosage of HCQ among 30 (60%) participants was 336.7 ± 30.3 g. The average duration of HCQ therapy was 5.1 years (min = 6 months, max = 82 months) in males and 6.2 years (min = 6 months, max = 110 months) in females. The mean cumulative dosage of CQ among 20 (40%) participants was 252.5 ± 28.3 g. The average duration of CQ therapy was 4.2 years (min = 8 months, max = 74 months) in males and 5.2 years (min = 11 months, max = 110 months) in females.

The mean measurements of P100 latency, amplitude of VEP, intraocular differential p100 latency, and mean intraocular differential p100 amplitude in our patients treated with HCQ were 109.5 ± 3.4 ms, 4.8 ± 3.6 mv, 3.5 ± 2.7, and 1.4 ± 1.1, respectively, and for patients treated with CQ were 110.5 ± 3.3 ms, 4.1 ± 3.4 mv, 3.5 ± 2.7, and 1.4 ± 1.1, respectively. Although in our results there was more affection in measures of VEP parameters in patients receiving CQ therapy compared with those receiving HCQ therapy, there was no statistically significant difference (*P* = 0.12, 0.4, 0.7, and 0.5, respectively).

The mean measurements of P100 latency, the amplitude of VEP, and of intraocular differential p100 latency in our patient group were 110.6 ± 4.4 ms, 4.1 ± 3.8 mv, and 3.5 ± 3.1, respectively, with significant difference compared with control group (*P* = 0.00, 0.00, and 0.03, respectively). However, there was no significant difference in mean intraocular differential p100 amplitude between patients and the control group, with *P* more than 0.05 (Table 1).

Our results showed that there was a statistically significant difference between percentage of patients and controls who had abnormal field of vision (*P* < 0.01); however, there was no statistically significant difference between percentage

Table 1: Demographic and visual evoked parameters of patients group receiving chloroquine/hydroxychloroquine therapy and control group

Parameters	Patients=50=100 eyes	Control=50=100 eyes	t	P
Age				
Mean±SD	40.8±9.9	38.9±9.7	11.370	0.017
Sex [n (%)]				
Female	43 (86)	40 (40)	0.79	0.42
Males	7 (14)	10 (10)		
P100 latency (ms) (mean±SD)	110.6±4.4	98.5±7.9	13.3	0.00
P100 amplitude (mv) (mean±SD)	64.1±3.8	8.2±7.05	5.1	0.00
P100 latency (IOD) (mean±SD)	3.5±3.1	2.4±4.1	2.1	0.03
P100 amplitude (IOD) (mean±SD)	1.5±1.1	0.77±2.9	2.35	0.19

HQ, hydroquinone; IOD, intraocular differential.

Table 2: The percentage of normal and abnormal readings in visual acuity, field of vision, and visual evoked potential of patients and controls

	Patients [n %]	Control [n %]	Difference (%)	95% CI		P
				Lower	Upper	
Visual acuity						
Normal	66 (66)	78 (78)				
Abnormal	34 (34)	22 (22)	12	5.514	18.48	0.06
Field of vision						
Normal	61 (61)	95 (95)				
Abnormal	39 (39)	5 (5)	34	24.5	43.4	<0.001
P100 latency						
Normal	43 (43)	98 (98)				
Abnormal	57 (57)	2 (2)	55	45.0	64.9	<0.001
P100 amplitude						
Normal	54 (54)	97 (97)				
Abnormal	46 (46)	3 (3)	43	33.12	52.87	<0.001
P100 latency (IOD)						
Normal	65 (35)	96 (96)				
Abnormal	35 (65)	4 (4)	31	21.71	40.22	<0.001
P100 amplitude (IOD)						
Normal	78 (78)	95 (95)				
Abnormal	22 (22)	5 (5)	17	9.5	24.4	<0.001
Cochran's Q P**	98.07-<0.001	69.21 0.001				

CI, confidence interval; IOD, intraocular differential.

Table 3: The sensitivity and specificity of the visual field and parameters of visual evoked potential

Parameters	Sensitivity (%)	Specificity (%)
Field of vision	39	95
P100 latency	57	98
P100 amplitude	46	97
P100 latency and amplitude	62	100
P100 latency (IOD)	35	96
P100 amplitude (IOD)	22	95

IOD, intraocular differential.

of patients having abnormal visual acuity and control group ($P = 0.06$), and there is no patient who had abnormality with fundus examination in both studied groups (Table 2). There was a statistically significant difference between the

percentage of patients and control group who had delayed P100 latency, low amplitude of P100 wave, abnormal P100 latency (IOD), and abnormal P100 amplitude (IOD), with $P < 0.001$ (Table 2).

Our results showed that there were 20 (33.3%) patients' eyes with abnormal visual acuity and 22 (36.6%) patients' eyes with abnormal field of vision treated with HCQ. Moreover, we found that 14 (35%) patients' eyes had abnormal visual acuity and 17 (42.5%) patients' eyes had abnormal field of vision treated with CQ. There were no statistically significant differences between percentages in both groups of patients ($P = 0.86$ and 0.52 , respectively).

There was a statistically significant difference between different tests (visual acuity, a field of vision, and VEP parameters) in patients receiving hydroquinone therapy and

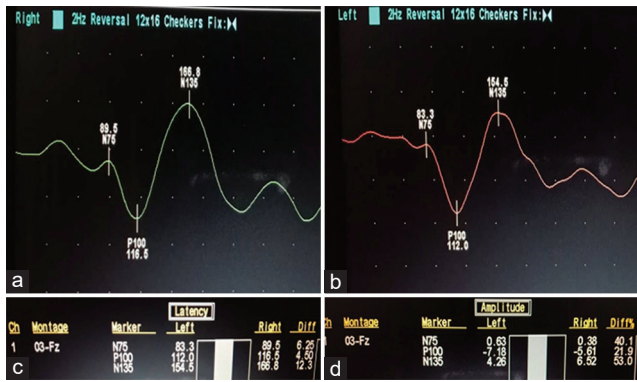


Figure 1: Visual evoked potential test of a female patient with rheumatoid arthritis receiving hydroxychloroquine for 7 years showed delayed p100 latencies of both eyes. (a) Right eye. (b) left eye. (c). latencies of VEP of both eyes. (d). amplitudes of VEP of both eyes.

in control group ($P < 0.001$), for both based on Cochran test (Table 2).

P100 latency was superior in sensitivity and specificity not only on the field of vision but also superior on other VEP parameters, and both P100 latency and amplitude increased the sensitivity of VEP test to 62% and specificity to 100%, as shown in Table 3.

P100 latency and P100 latency (IOD) of VEP is significantly correlated with duration of treatment with antimalarial drugs ($r = 0.529, P < 0.001$ and $r = 0.285, P = 0.04$, respectively). However, there is no significant correlation between duration of treatment and other VEP parameters (P100 amplitude and P100 amplitude (IOD) ($r = -0.04$ and $P = 0.69$, and $r = -0.12$ and $P = 0.87$, respectively) (Figs. 1 and 2).

DISCUSSION

HCQ is used widely to manage connective tissue and skin disorders owing to lower adverse effects compared with CQ [13]. Although long-term use of both has various adverse effects, a major concern is their effect on different ocular structures including ciliary body involvement, crystalline lens opacity, as well as retinopathy and keratopathy. So, it is necessary to perform regular eye screening programs using the best test possible with more sensitivity and good power for early detection and prevention of HCQ ocular toxicity [14].

Our study showed the mean P100 latency of the patients receiving antimalarial therapy was 110.6 ± 4.4 ms and was significantly higher than healthy controls ($P < 0.001$). This result was in agreement with other studies of 100 patients with RA receiving hydroquinone therapy and 100 healthy control group, where they found that the mean P100 latency was 112.7 ± 10.1 ms among the patients, which was also significantly higher than controls ($P < 0.001$) [15].

Overall, 57% of our cases who used CQ/HCQ (27% receiving CQ and 30% receiving HCQ) had P100 latency higher than 110 ms. Similar results were found by other authors. They

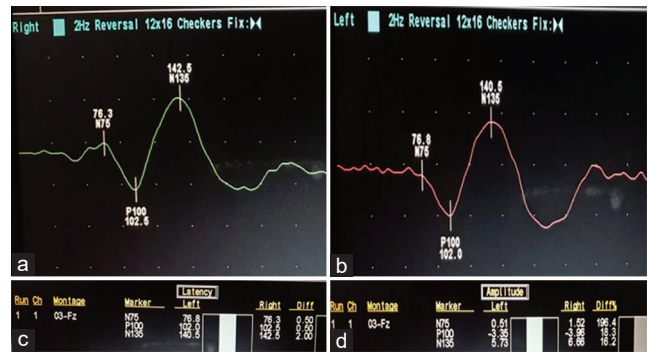


Figure 2: Visual evoked potential test of a male patient with rheumatoid arthritis receiving hydroxychloroquine for 10 years showed amplitudes of p100 of both eyes. (a). Right eye. (b). left eye. (c). latencies of VEP of both eyes. (d). amplitudes of VEP of both eyes.

compared VEP and electrooculogram (EOG) tests in early detection of hydroquinone retinal toxicity. They performed a prospective cross-sectional study on 100 patients with RA, with an age range of between 18 and 38 years. They found 65% of their patients had P100 latency higher than 110 ms [16]. It means that CQ/HCQ can prolong the P100 latency of VEP test which is the most reliable indicator of abnormality, as it is the least affected by patient cooperation and technical factors.

Heravian *et al.* [10] in agreement with our study. They made a comparative study on the usefulness of color vision PSRT, and VEP test in early detection of ocular toxicity from HCQ, and they found that in the early stages of maculopathy, P100 latencies of VEP and PSRT are useful predictors of HCQ ocular toxicity, and moreover, in patients without ocular symptoms and fundoscopic changes, the P100 latency of VEP predicts more precisely than the others.

However, Bartel and Roux [17] believed that VEP is not a suitable test for screening of HCQ, and Bishara and Matamoros [18] have stated that VEP is unable to detect ocular toxicity owing to HCQ as good as a contrast sensitivity test.

Our study showed the mean P100 amplitude was 4.1 ± 3.8 mv and was significantly lower than control group ($P < 0.001$). This is similar to another study, where they found that the mean P100 amplitude was 3.7 ± 2.1 mv, and it was significantly lower than controls ($P < 0.001$) [16]. However, Heravian and colleagues found no statistically significant difference between mean P100 amplitude in their case and control groups with the age range of 20–50 years old [4]. This difference can be attributed to the fact that amplitude is an indicator of clinical abnormality and is more prone to be affected by technical factors, patients fixation, cooperation, and alertness [10].

Our study showed 46% of our cases had low P 100 amplitude compared with P100 latency (57%). Moreover, another study found that 59% of their cases had low P100 amplitude (59%) compared with P100 latency (65%). Recently, the authors disagree with our results and stated that the P100 amplitude is the most commonly observed abnormal VEP parameter. This contradiction may be caused by the different method of

calculation being concerned by the difference between the two eyes and calculating the difference in ratio [19].

Another study also disagreed with our result. It studies 30 patients with RA who underwent HCQ treatment, and a control group included normal population. The mean latency of VEP, P100 peak/SD were 98/8.15 and 102/9.20 (ms) in control and case groups, respectively. The mean amplitudes of VEP, P100 peak/SD were 8.2/2.25 and 7.4/2.18 μ v in control and case groups, respectively. The differences between mean latency and amplitude of VEP, P100 peak were not statistically significant. They conclude that HCQ does not affect visual pathway, which can be proved using VEP [20].

Our results also showed that there was a statistically significant difference between different tests (visual acuity, a field of vision, and VEP parameters) in patients receiving CQ/HCQ therapy and in control group ($P < 0.001$, for both).

In another study, the readings compared of EOG and VEP tests in 100 patients with RA (mean age: 23.5 ± 2.8 years) to determine the test with more sensitivity for a screening of HCQ toxicity. Most participants (80% of cases) were female. The mean measurement of Arden Index score (EOG), P100 latency, and amplitude of VEP were 1.8 ± 0.4 , 112.7 ± 10.1 ms, and 3.7 ± 2.1 mv, respectively. There was a statistically significant difference between case and control groups in all parameters ($P < 0.01$). There was not any significant difference between AI (EOG), P100 latency, and amplitude of VEP in detecting the ocular toxicity owing to HCQ [16].

Moreover, we found that P100 latency of VEP was superior in sensitivity and specificity not only on the field of vision but also superior on other VEP parameters to detect HCQ retinal toxicity, and both P100 latency and amplitude increased the sensitivity of VEP test to 62% and specificity to 100%.

Our study findings were also consistent with Paulose and colleagues who found that change in Humphrey 10–2 VFs should be thoroughly evaluated with additional objective testing because paracentral scotomas diagnosed with VF examination are found in advanced or late disease [5]. The simplest explanation was that the patient was not a good field taker so the VHF were not reliable. He also claimed that when it comes to the diagnosis and treatment of optic neuritis, VEP has clear advantages over traditional VFs [21].

In the same vein comes the study adopted by Andersson and Sidén [22], where they analyzed various VEP parameters in 126 patients with multiple sclerosis, isolated optic neuritis, or isolated myelopathy. The single most common deviation in eyes with clinical evidence of optic neuritis was a prolongation of the latency to P100 with the highest sensitivity.

Nebbos *et al.* [11] studied VEP as a traditional method and multifactorial VEP (mfVEP) in 24 patients versus automated perimetry frequency doubling technology matrix (FDT) and found that pattern-reversal VEP is the most sensitive and

practical diagnostic tool in the diagnosis of the patient with ON with sensitivity of 90.9%.

In our study, we found that in VEP studies there is increased in both the absolute and interocular differential latency of P100 wave in our patients who receiving CQ/HCQ therapy for a long duration. These findings were in agreement with Silvio P N, who also found that the most common changes in VEP studies in optic neuritis with increased duration of treatment were as follows: increased interocular differential latency of P100 wave and the absolute increase in latency of P100 wave.[23]

Coming with this result, Hood *et al.* [24] found that interocular results were consistent with a linear relationship between the amplitude of the signal portion of the VEP response and linear HVF loss. They pointed to a qualitative agreement between regions of decreased mfVEP amplitude and regions showing HVF defects.

Interocular comparison techniques have been proposed as a better way to quantify and detect damage. Interocular comparisons of mfVEPs have been used to identify local damage in patients with optic neuritis [25].

In recent years, other ocular assessments, using multifocal electroretinogram and full-field electroretinogram, have proved to be useful in screening of HCQ toxicity, especially for those patients with longer disease duration, longer duration of HCQ treatment, higher cumulative dosages, and older ages.

Finally, we conclude that P100 latency of VEP can be useful parameter to detect CQ/HCQ retinal toxicity and was superior in sensitivity and specificity not only on field of vision but also on other VEP parameters, and both the absolute and interocular differential latency of P100 wave of VEP are significantly correlated to duration of treatment; however, both fields of vision examination and P100 amplitude parameters are inferior changes.

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Conflicts of interest

There are no conflicts of interest.

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