Original Article

Comparison of Visual Evoked Potential and Electro-OculogramTests in Early Detection of Hydroxychloroquine Retinal Toxicity

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Abstract

Purpose: To compare the sensitivity of visual evoked potential (VEP) and electro-oculogram (EOG) tests in early detection of hydroxychloroquine (HCQ) retinal toxicity.

Patients and Methods: In this prospective cross-sectional study, 100 consecutive patients (age range: 18 to 30 years) with juvenile rheumatoid arteritis (JRA) and a cumulative hydroxychloroquine dosage of at least 200 gr were included. In addition 100 healthy individuals with matched age and sex were included as controls. Ocular examinations including visual acuity testing, refractive errors measurement, applanation tonometry, slit lamp biomicroscopy fundus ophthalmoscopy and electrophysiological examinations (EOG and VEP) were performed in both groups. Scores of less than 1.8 for the Arden Index in EOG (AI), as well as less than 4mv of P100 amplitude and more than 110ms of P100 latency in VEP were considered abnormal.

Results: The mean cumulative dosage of HCQ among participants was 262.4 ± 31.9 g (95 % CI: 256.1 to 268.8 g). The mean measurement of AI (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 significant difference between case and control groups in all parameters ($P < 0.001$ for all). There was not any significant difference between AI (EOG), P100 latency and amplitude of VEP in detecting the ocular toxicity due to HCQ.

Conclusion: We conclude that AI (EOG), P100 amplitude and latency of VEP can all be useful parameters to detect HCQ retinal toxicity and we did not detect any difference between these methods.

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Introduction

Chloroquine and hydroxychloroquine (HCQ) are generations of 4-aminoquinoline antimalarial compounds [1], which are used to treat patients with rheumatoid arthritis (RA), systemic lupus erythematosus, dermatomyositis, Sjogren's syndrome and other connective tissue diseases since the 1950s [2, 3]. Although long term use of both has various side effects such as gastro-intestinal 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 [2-6]. Also major effects on retina causing permanent visual loss have been reported [7, 8]. Therefore early detection of ocular side effects due to HCQ is necessary to prevent consequent serious ocular problems [9]. Different ocular tests have been used to screen patients taking anti-malarial drugs including visual acuity testing, dilated funduscopy, visual field testing, fundus photography, fluorescein angiography, color vision testing and electrophysiological tests, but their efficiency is controversial [10-13]. Some studies have compared different visual tests in order to indicate the best test for screening [1, 4, 9, 10, 14]. Some authors report that contrast sensitivity has the most sensitivity and efficiency compared with other considered tests [9], but others have found a P100 latency of visual evoked potential (VEP) and photostress recovery time tests to be the best predictors in early stages of maculopathy, with the P100 latency of VEP being the best predictor in patients without ocular symptoms and fuduscopic lesions [4]. A study by Neubauer et al. suggests a sensitive color vision test can be useful in screening of chloroquine retinopathy [10]. Others have suggested the evaluation of central visual field as the best test for the early diagnosis of HCQ toxicity [2, 12]. Although fluorescein angiography has been suggested to have less importance in diagnosis of early retinopathy, it is useful in patients who find visual field testing difficult [2, 15].

It has been observed that HCQ causes perifoveal changes in retinal pigmented epithelium layer (RPE) [4, 16] which induces abnormal readings in Electro-oculography [9] and visual evoked potential [16]; therefore we decided to compare the sensitivity between these two electrophysiological tests, since they can assess visual function objectively against the other suggested subjective tests, so their results can be more reliable.

Electro-oculography (EOG) is a type of electrophysiologic test which measures the corneo-retinal standing potential that exists between the front and the back of the human eye. It does not measure the response to individual visual stimuli but shows the interaction between RPE and rod cells [17]. EOG has been introduced as a sensitive test to indicate the functional disturbance due to storage of HCQ in RPE [18], although its usage is still controversial [19]. VEP refers to electrical potentials, initiated by either patterned or unpatterned visual stimuli, which are recorded from the scalp overlying the visual cortex [20]. VEPs are used primarily to measure the functional integrity of the visual pathways from retina via the optic nerves to the visual cortex of the brain [20].

In the present study we compared VEP and EOG tests for detecting HCQ toxicity before the presence of ocular symptoms.

Patients and Methods

In this prospective cross sectional study a total of 100 consecutive patients with and a history

of hydroxychloroquine usage were examined in Basir Eye Clinic, Tehran, Iran from June 2013 to May 2014. The study was approved by the Local ethics commitee, and a written consent was signed by all participants or their legal guardians before entering the study. The inclusion criteria was age of 17 to 30 years, a history of confirmed Juvenile rheumatoid arthritis (JRA), best corrected visual acuity of 20/20 or better at both near and far distances, not having any obvious lesions on their funduscopic examinations, cumulative dosage of at least 200 grams calculated based on the patients' daily dose and duration. This was selected according to recommendation of the College of Ophthalmologists that suggests requirement of ophthalmic monitoring for patient with cumulative dosage higher than 200 grams [21, 22]. The exclusion criteria were any other causes for macular changes such as diabetes, central serous retinopathy, retinitis pigmentosa, age macular degeneration, any history of taking ophthalmic or systemic medications with an effect on the electrophysiologic tests readings, any history of ocular surgery, and other anterior or posterior segments ophthalmic diseases. The control group included 100 age and sex matched healthy individuals.

A comprehensive ocular examination including visual acuity testing, refractive errors measurement, applanation tonometry, slit lamp biomicroscopy as well as direct and indirect fundus ophthalmoscopy were performed on all cases and controls.

Electrophysiological examinations were performed using EOG and VEP tests in both groups.

Electro-oculography (EOG)

Electro-oculography was performed in accordance with the standards of International Society for Clinical Electrophysiology of Vision (ISCEV). Pupil dilation was performed using 1 % tropicamide before pre-adaptation. Horizontal fixation targets were 30º apart and silver-silver chloride electrodes were placed according to ISCEV standards. Recording was performed using a Jaeger-Toennies system (Hoechberg, Germany) and the Arden ratio (Arden quotient, AQ) between the lowest dark adapted point and highest light point was calculated. A score of less than 1.8 for the Arden Index (AI) was considered abnormal [9].

Visual Evoked Potential (VEP)

VEP wave forms were recorded. The black and white size was 40 min of arc at a viewing distance of 1 m. In recording pattern VEP (PVEP), the active electrode was positioned 2.5 cm above the inion (Oz), referenced to the center of the forehead with a ground electrode on the vertex of the head. All tests were performed with the subjects wearing their best refractive correction. The scores of less than 4 mv of P100 amplitude and more than 110 ms of P100 latency were considered abnormal [9].

Sample Size Calculation and Statistical Analysis

To have a power of 95 % to detect 1 unit difference in amplitude when the standard deviation of the amplitude was estimated to be 1.95 a sample size of 99 was needed. We entered 100 samples in each group. To describe data we used mean, standard deviation, median and range. To check the normal distribution of data we used Kolmogorov test with Q-Q plot and histogram. To evaluate the difference between two groups we used t-test, Mann-Whitney test and Chi-square test. Also, 95 % confidence interval (CI) was used to illustrate this difference. All statistical analysis was performed by SPSS (Version 17, SPSS Co., Chicago, IL). P values less than 0.05 were considered statistically significant.

Results

In the present study the readings of EOG and VEP

tests were compared in 100 patients with JRA (mean age: 23.5 ± 2.8 years) in order to determine the test with more sensitivity for screening of HCQ toxicity. Most participants (80 % of cases) were female. The mean cumulative dosage of HCQ among participants was 262.4 ± 31.9 g (95 % CI: 256.1 to 268.8 g).

Table 1 summarizes the demographic characteristics of all participants. The mean measurement of AI (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 ($P < 0.001$ for all).

Table 2 shows number of normal and abnormal readings in the case group according to criteria indicated previously. A high number of our cases in all considered parameters were out of the normal limit. There was not any statistically significant difference between AI (EOG), P100 latency and amplitude of VEP in detecting the ocular toxicity due to HCQ.

Figure 1 presents the percentage of normal and abnormal readings of AI of EOG, P100 latency and amplitude of VEP among cases. As shown 65 %, 59 % and 49 % of patients were out of the normal limits according to P100 latency and amplitude of VEP as well as AI (EOG), respectively.

Table 1: Demographic findings in the case and control groups.

	Level	Total	Case	Control	P
Age	Mean ± SD	23.4 ± 2.6	23.5 ± 2.8	23.4 ± 2.5	0.725 †
	Median (range)	23 (17 to 30)	23 (18 to 30)	23 (17 to 28)	
Sex	Female	157 (78.5 %)	80 (80.0 %)	77 (77.0 %)	0.606 *
	Male	43 (21.5 %)	20 (20.0 %)	23 (23.0 %)	
EOG(AI)	Mean ± SD	2 ± 0.5	1.8 ± 0.4	2.2 ± 0.3	< 0.001 †
	Median (range)	2.1 (1.1 to3.1)	1.8 (1.1 to 3)	2.2 (1.4 to 3.1)	
Latency	Mean ± SD	107.4 ± 9.4	112.7 ± 10.1	102.1 ± 4.1	< 0.001 §
	Median (range)	104 (92 to135)	115 (94 to 135)	102 (92 to 112)	
Amplitude	Mean ± SD	4.9 ± 2.3	3.7 ± 2.1	6.2 ± 1.6	< 0.001 §
	Median (range)	5 (1 to 10)	3 (1 to 8)	6 (1 to 10)	

EOG: electro-oculogram; AI: arden index; SD: standard deviation; P: probability
† Based on t-test.
* Based on Chi-Square test.
§ Based on Mann-Whitney test.

Table 2: The percentage of normal and abnormal readings in EOG and VEP of patients and controls.

		Group		Difference	95 % CI		P *
		Case	Control		Lower	Upper	
EOG (AI)	Normal	51 (51.0 %)	94 (94.0 %)				
	Abnormal	49 (49.0 %)	6 (6.0 %)	43.0 %	32.2 %	53.8 %	< 0.001
Latency	Normal	35 (35.0 %)	98 (98.0 %)				
	Abnormal	65 (65.0 %)	2 (2.0 %)	63.0 %	53.3 %	72.7 %	< 0.001
Amplitude	Normal	41 (41.0 %)	96 (96.0 %)				
	Abnormal	59 (59.0 %)	4 (4.0 %)	55.0 %	44.6 %	65.4 %	< 0.001
P **		0.092	0.368				

EOG: electro-oculogram; AI: arden index; CI: confidence interval; P: probability.
* Based on Chi-Square test.
** Based on Cochran test.

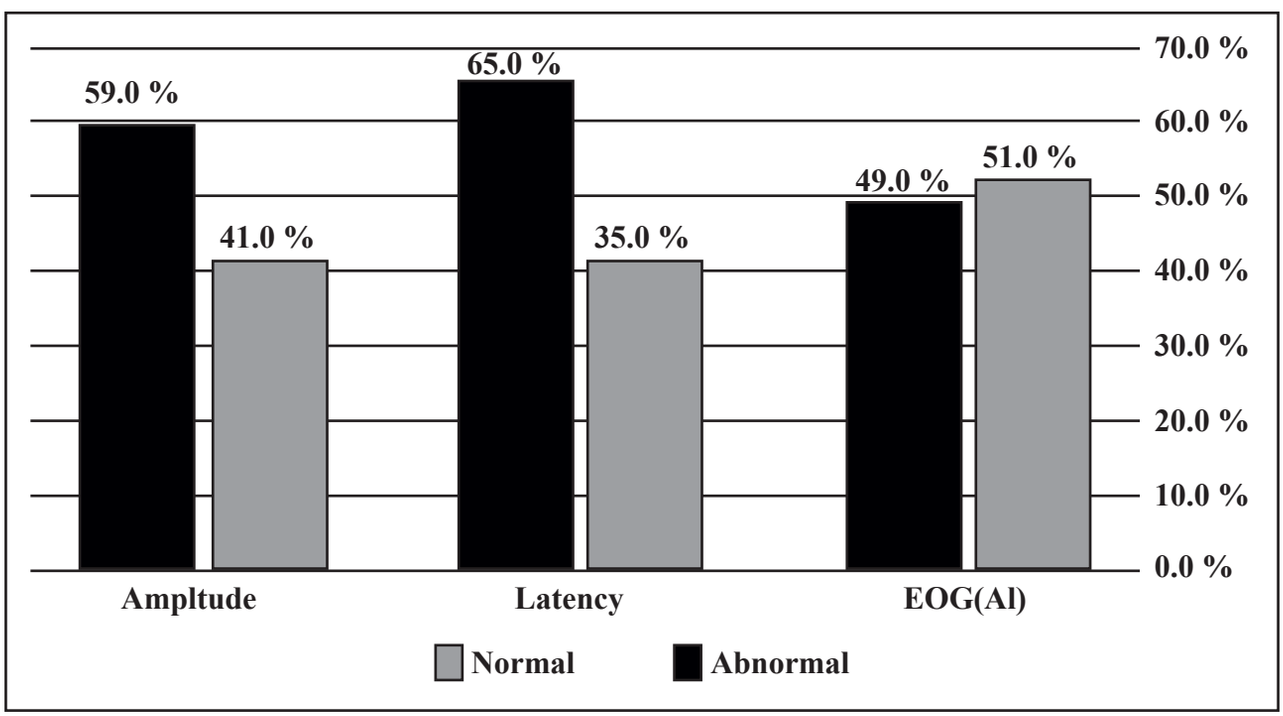

Figure 1: The distribution of normal and abnormal readings in EOG (AI) as well as latency (VEP) and amplitude (VEP) among patients.

Discussion

Nowadays HCQ is used widely in order to manage connective tissue and skin disorders due to lower side effects compared to chloroquine [2]. It is necessary to perform regular eye screening programs using the best test possible with more sensitivity and a good power for early detection and prevention of HCQ ocular toxicity [4]. We only entered patients with JRA in the age range of 17 to 30 years old to eliminate the effect of senile changes like the accumulation of lipofuscein deposits that might affect the electrophysiological readings.

Although the American Academy of Ophthalmology guidelines considers patients with HCQ duration usage of less than 5 years to be at a lower risk of toxicity [12], majority of our patients showed readings out of the normal limitations (Table 2). Bishara et al. studied patients who took HCQ for periods ranging from 1 to 9 years and found that EOG cannot detect the early ocular toxicity as good as contrast sensitivity test [9]. In a study Neubauer et al. [10] compared EOG versus color vision test to indicate the one with more sensitivity to evaluate early ocular changes due to chloroquine and HCQ usage. They found color vision test to be a more sensitive test for screening, but EOG showed little diagnostic value in this regard.

The mean P100 latency was 112.7 ± 10.1 ms among our cases and it was significantly higher than controls ($P < 0.001$) similar to other studies [1, 4, 9]. Sixty five percent of our cases who used HCQ had P100 latency higher than 110 ms. It means that HCQ can prolong the P100 latency of VEP test which is the most reliable indicator of abnormality since it is least effected by patient cooperation and technical factors [20]. Heravian et al. [4] have indicated P100 latency as the best predictor of HCQ ocular toxicity in patients without ocular symptoms and fundoscopic changes and have reported that it can predict early stages of HCQ maculopathy.

Fifty nine percent of our cases had abnormal P100 amplitude, the mean was 3.7 ± 2.1 mv and it was significantly lower than controls ($P < 0.001$). However Heravian et al. found no statistically significant difference between P100 amplitude in their case and control groups with the age range of 20 to 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 [20].

Bartel et al. [14] believed that VEP is not a suitable test for screening of HCQ and Bishara et al. [9] have stated that VEP is unable to detect ocular toxicity due to HCQ as good as contrast sensitivity test. We found that VEP and EOG can both determine early changes due to HCQ ocular toxicity in more than half of our patients.

Conclusion

We conclude that AI (EOG), P100 amplitude and latency of VEP can all be useful parameters to detect HCQ retinal toxicity and we did not detect any difference between these methods.

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Footnotes and Financial Disclosures

Conflict of Interest:

The authors declare no conflict of interest with the subject matter of the present manuscript.