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ÖZGÜN ARAŞTIRMA/ORIGINAL ARTICLE

Hidroksiklorokin Kullanan Retinal Toksisite Gelişmemiş Hastalarda Koroid Kalınlığı

Choroidal Thickness in Patients Using Hydroxychloroquine Without Retinal Toxicity

Hayati Yılmaz[1] ORCID no: 0000-0001-5051-5713, **Dorukcan Akıncıoğlu**[2] ORCID no: 0000-0001-6409-9802, **Murat Küçükevcilioğlu**[3] ORCID no: 0000-0001-7776-2183, **Gökhan Özge**[3] ORCID no: 0000-0003-0943-8917, **Ali Hakan Durukan**[3] ORCID no: 0000-0001-6571-6155, **Fatih Mehmet Mutlu**[3] ORCID no: 0000-0002-7796-6511

[1] Hitit University Medical Faculty, Department of Ophthalmology, Corum, Turkey.
[2] Atatürk State Hospital, Department of Ophthalmology, Antalya, Turkey.
[3] Health Sciences University, Gulhane Medical Faculty, Department Of Ophthalmology, Ankara, TURKEY.

Geliş Tarihi/Received: 23.09.2020
Kabul Tarihi/Accepted: 20.10.2020
Yazışma Adresi/Address for Correspondence:
Hayati Yilmaz, M.D.
Hitit University,
Medical Faculty,
Department of Ophthalmology.
e-posta: dr.hyilmaz@hotmail.com

Anahtar Sözcükler:
Hidroksiklorokin
Koroid kalınlığı
Optik koherens tomografi

ÖZ

Amaç: Hidroksiklorokin erken dönemde tespit edilmezse kalıcı retinal hasara sebep olabilen, iyi bilinen, antiromatizmal bir ilaçtır. Buna rağmen koroid tabakasına etkisini araştıran herhangi bir çalışma bulunmamaktadır. Bu çalışmada biz hidroksiklorokinin submaküler koroid kalınlığına etkisini değerlendirmeyi amaçladık.

Gereç ve Yöntem: Otuz (n:30) hidroksiklorokin kullanan hasta ve otuz dokuz (n:39) sağlıklı kontrol çalışmaya dahil edildi. Analizlerde yalnızca sağ gözler kullanıldı. Hasta ve kontrollerin demografik verileri kayıt edildi. Tüm hastaların refraksiyon, görme keskinliği, göz içi basıncı, 10-2 görme alanı testi, biyomikroskopi ve fundoskopik muayenelerini içeren oftalmolojik muayene bulguları kayıt edildi. Son olarak ise submaküler koroid kalınlığı arttırılmış derinlik görüntüleme-optik koherens tomografi (EDI-OKT) yöntemi ile 5 noktadan (subfoveal, nazal500, nazal1500, temporal500 ve temporal1500) ölçüldü.

Bulgular: Yaş, cinsiyet, göz içi basıncı ve görme keskinliği açısından gruplar arası anlamlı fark yoktu ($P > 0,05$). Ölçüm yapılan tüm noktalarda koroid kalınlığı hidroksiklorokin kullananlarda kontrollere göre istatiksel daha kalın idi (subfoveal; $p < 0,05$, nazal 500; $p < 0,01$, nazal 1500; $p < 0,01$, temporal 500; $p < 0,01$,temporal 1500; $p < 0,01$). Hasta grubunda subfoveal ortalama koroid kalınlığı 319,2 ± 79,4 idi, kontrol grubunda ise 270.3 ± 102.4 idi. Nazal 500 noktasında 314,3 ± 84,7'a karşılık 253,7 ± 94,8, nazal 1500 noktasında 288 ± 90,1'a karşılık 219,8 ± 84,4, temporal 500 noktasında 313,9 ± 76,1'a karşılık 254,4 ± 90,9 ve temporal 1500 noktasında 288,6 ± 61,3'a karşılık 240,9 ± 90,7 idi.

Sonuç: Submaküler koroidin kalınlaşması hidroksiklorokinin koroidal melanositlerde birikmesine ve çevre dokudaki reaksiyona bağlı olabilir. Bu hipotezin doğrulanabilmesi için deneysel çalışmalar gerekmektedir.

Key Words:
Hydroxychloroquine
Choroidal thickness
Optical coherence tomography

ABSTRACT

Objective: Hydroxychloroquine is a well-known antirheumatic drug that may cause irreversible retinal damage if not detected earlier. However, to date there has been no study investigating the effects of hydroxychloroquine on the choroid. In this study we evaluated the submacular choroidal thickness in patients using hydroxychloroquine without retinal toxicity in comparison to healthy controls.

Material and Method: Thirty patients (n:30) using hydroxychloroquine, and thirtynine healthy controls (n:39) were included in this study. Only right eyes of the patients and the control subjects were used in the analysis. Demographic features of the patients and control subjects were recorded. Each subject underwent ophthalmological examinations including refraction, visual acuity, intraocular pressure, 10/2 visual field testing, slitlamp biomicroscopy, and fundus examination. As the last step submacular choroid was imaged by enhanced depth imaging optical coherence tomography (EDI-OCT), and measured manually at five regions (subfoveal, nasal 500, nasal 1500, temporal 500 and temporal 1500).

Yılmaz H., Akıncıoğlu D, Küçükevcilioğlu M, Özge G, Durukan AH, Mutlu FM. Choroidal Thickness in Patients Using Hydroxychloroquine Without Retinal Toxicity. Hitit Med J 2020;2(3): 73-78.

Results: There were no significant differences between patients and controls regarding age, gender, intraocular pressure, best-corrected visual acuity (p>0,05). Choroidal thickness values at all regions were statistically higher in patients than controls (subfoveal; $p < 0.05$, nasal 500; $p < 0.01$, nasal 1500; $p < 0.01$, temporal 500; $p < 0.01$,temporal 1500; $p < 0.01$). The mean of the subfoveal choroidal thickness is 319.2 ± 79.4 in patients and 270.3 ± 102.4 in controls. It is 314.3 ± 84.7 vs 253.7 ± 94.8 for nasal 500, 288 ± 90.1 vs 219.8 ± 84.4 for nasal 1500, 313.9 ± 76.1 vs 254.4 ± 90.9 for temporal 500 and 288.6 ± 61.3 vs 240.9 ± 90.7 for temporal 1500.

Conclusion: Thickening in submacular choroid could be due to accumulation of these drugs in the choroidal melanocytes and reactions from the surrounding tissues.

Introduction

Hydroxychloroquine (HCQ) is broadly used in the handling of several rheumatic conditions, including systemic lupus erythematosus and rheumatoid arthritis (1,2). This medicine also has possible utility in diabetes mellitus, heart disease, cancer therapy and even in COVID-19 related pneumonia. Therefore, the number of people using the medication is anticipated to increase (1). HCQ retinopathy is a well-documented side effect of HCQ and is described by bilateral bulls-eye maculopathy, which gives as a ring of parafoveal retinal pigment epithelium depigmentation that spares the fovea (1,2). The American Academy of Ophthalmology (AAO) recently revised the guidelines for screening, including visual field examination, fundus autofluorescence (FAF), multifocal electroretinogram (mfERG), and optical coherence tomography (OCT) assessment (1).

The pathogenesis of HCQ retinopathy is not understood entirely. Previous studies have recommended that HCQ affects the metabolism of retinal cells, or that it includes a breakdown of the blood-retinal barrier (3). However, these hypotheses have not been intensely supported or confirmed. Even it is believed that HCQ has protecting effect against the diseases like age-related macular degeneration (4).

Although the inner retina is not impaired significantly in eyes with HCQ-related toxicity, the photoreceptors and RPE can show notable degeneration (5-7). The outer retinal layers are fed by the choroid, more precisely, the choriocapillaris. The retinal pigment epithelium (RPE) layer, which is defective in HCQ retinopathy, plays a crucial role in the integrity of the choriocapillaris. It is also known that HCQ has an affinity for melanocytes, and melanocytes are most frequently found in choriocapillaris and RPE in the eye (8,9), therefore, we hypothesized that the HCQ which is used for the treatment of several diseases may also affect the choroid. To evaluate the effect of HCQ on the choroid, we compared the choroidal thickness between the patients using HCQ but without HCQ retinopathy and healthy controls. We also checked for the associations of HCQ daily and cumulative dosage with the choroidal thickness (CT).

Material and Method

Demographic data and clinical findings

This study was carried out in accordance with the principles of the Declaration of Helsinki after obtaining the approval of the Clinical Research Ethics Committee of the Hitit University, Turkey. Included in the study were the patients using HCQ that presented to the outpatient clinics of Ophthalmology Department of Gülhane Medical Faculty, in the period of February 2016 to February 2018, for the screening of HCQ retinopathy, and age and sex-matched healthy subjects that presented for routine refraction examination who had undergone a complete ophthalmological examination, including LogMAR-converted best-corrected visual acuity (BCVA) and intraocular pressure (IOP) measurements, slit-lamp biomicroscopy, and non-dilated fundoscopy along with macular analysis using spectral domain-OCT (SD-OCT) scans (Spectralis II, Heidelberg Engineering, Heidelberg, Germany) during the same visit. The patients using HCQ also had visual field (VF) testing (Humphrey Field Analyzer II, Humphrey-Zeiss Instruments, Dublin, CA, USA). The exclusion criteria were age under 18 years, refractive error of ≥ 3 diopters, presence of any other ophthalmological pathology (e.g., diabetes or hypertensive retinal diseases, amblyopia, optic nerve abnormalities, glaucoma, and age-related macular degeneration) or a history of ocular surgery (including cataract and glaucoma surgery) that could confound the assessment results, and OCT signal strength of < 20. The patients with HCQ retinopathy were also excluded from the study.

Age, gender, ethnic background along with the time period of the usage of HCQ, the daily dosage of HCQ, and the cumulative dose of HCQ were recorded.

Macular Analysis

Spectralis OCT (version 4.0) (Heidelberg Engineering, Heidelberg, Germany) was used for the measurement of RNFL thickness (RNFLT). This device has an A-scan rate of 40,000/s using a light source of 820 nm. All images were acquired using the EDI mode with 6 radial B-scans centered on the fovea. Image quality was judged based on the signal-to-noise ratio, and only scans with signal-to-noise ratio > 20 dB were saved and considered for analysis. CT measured manually by an experimented retina specialist (HY) from 5 separate regions in the central foveal scan; subfoveal, 500 microns nasally from the fovea (nasal 500), 1500 microns nasally from the fovea (nasal 1500), 500 microns temporally from the fovea (temporal 500) and 1500 microns temporally from the fovea (temporal 1500). The inner segmentation line was placed on the RPE/Bruch's membrane interface and the outer segmentation line was placed on the sclerochoroidal interface to represent the inner and outer boundaries of the choroid in each B-scan image (Figure 1).

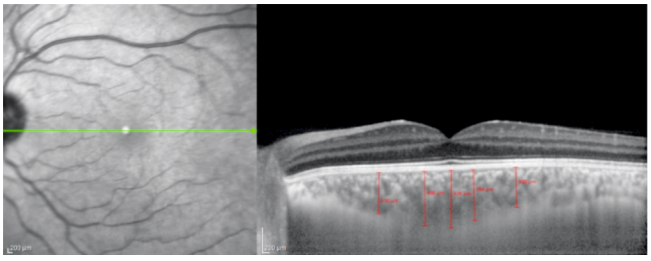

Figure 1: Choroidal thickness measurement with enhanced depth imaging at the regions of subfoveal, nasal500 µm, nasal1500µm, temporal 500µm, temporal1500µm.

Statistical Analysis

Quantitative variables were described as mean and standard deviation (SD), and qualitative variables as percentages. Power calculation was not executed as the study was exploratory. The individuals with missing data were excluded from the analyses. The Shapiro-Wilk test was used to determine whether the sample came from a normally distributed population. According to the results of the normality test, Student's t-test or Mann-Whitney U test was used to compare the patients using HCQ and the controls. Associations of the CT with HCQ daily dosage and cumulative dose were searched, independent from age and gender, using linear regression models. Regression results were given with coefficient (B), 95% confidence interval (CI), and P values. A P value less than 0.05 considered significant.

Results

Demographic data and clinical findings

Thirty patients using HCQ of 34 and 39 controls of 41 were met the inclusion criteria. Four patients using HCQ were excluded from the study due to having a history of ocular surgery (n = 1), retinal degenerative disorder (n = 1), and HCQ retinopathy (n = 2). Two of the control patients were excluded from the study due to having high myopia (n = 1) and hypermetropia (n = 1). Twenty one of the 30 patients had been using HCQ due to rheumatoid arthritis and 9 of them due to systemic lupus erythematosus. The mean age of the patients using HCQ was 52.4 ± 13.9 years and it was 50.2 ± 11.9 years for the control subjects. The difference was not significant (P = 0.114, student *t*-test). The gender distribution was similar between the groups with 27 (90 %) female patients using HCQ and 34 (87.1 %) female controls (P = 0.223, Pearson's chi-square test). The demographic data and the clinical findings of the study participants were presented in Table 1.

Table 1: Demographic And Clinical Features Of Study Subjects
SD: Standard Deviation,
LOP: Intra-ocular Pressure,
SLE: Systemic Lupus Erythematosus,
RA: Rheumatoid Arthritis,
HCQ: Hydroxychloroquine,
N/A: Not Applicable.
**The Results of the Student T-test.*
***The Results of the Pearson's Chi Square Test.*

	Patients	Controls	P
AGE (YEARS ± SD)	52.4 ± 13.9	50.2 ± 11.9	0.114*
FEMALE (N/%)	27/90	34/87	0.223**
IOP (MMHG ± SD)	14.4 ± 2.9	15.1 ± 3.1	0.245*
SLE/RA (N)	9/21	n/a	n/a
HCQ DAILY DOSE (MG/RANGE)	313.33/200-400	n/a	n/a
HCQ CUMULATIVE DOSE (G ± SD)	1058 ± 540.97	n/a	n/a

The mean/median/range daily dosage of the HCQ that the patients get were 313.33/400/200-400 mg. The mean cumulative dose of the HCQ was 1058 ± 540.97 g.

Choroidal thickness results

CT measurements of 5 different regions are given in Table 2. The mean CTs of the subfoveal, nasal 500, nasal 1500, temporal 500, and temporal 1500 regions

Table 2: The Ct Measurements Of The Study Subjects.
CT: Choroidal Thickness.
**The Results of the Student T-test. Significant P Values Are Expressed With Bold Style.*

CT REGION	Patients	Controls	P*
SUBFOVEAL (µM ± SD)	319.2 ± 79.4	270.3 ± 102.4	**0.031**
NASAL 500 (µM ± SD)	314.2 ± 84.7	253.7 ± 94.8	**0.007**
NASAL 1500 (µM ± SD)	288 ± 90.1	219.8 ± 84.4	**0.002**
TEMPORAL 500 (µM ± SD)	313.9 ± 76.1	254.4 ± 90.9	**0.004**
TEMPORAL 1500 (µM ± SD)	288.6 ± 61.3	240.9 ± 90.7	**0.007**

were 319.2 ± 79.4, 314.3 ± 84.7, 288.0 ± 90.1, 313.9 ± 76.1 and 288.6 ± 61.3 µm, respectively for the patients using HCQ. CTs of the corresponding regions of the healthy controls were 270.3 ± 102.4, 253.7 ± 94.7, 219.8 ± 84.4, and 240.9 ± 90.7 µm, respectively. The CTs of the patients using HCQ were differed significantly from the CTs of the healthy controls (P = 0.031, 0.007, 0.002, 0.004, and 0.007, respectively).

Cts of all regions were found associated with cumulative dose of the HCQ but not with the daily dosage independent from gender and age. The associations are presented in Table 3.

Table 3: The Multiple Regression Models' Results Of The Study Subjects.
HCQ: Hydroxycholoroquine,
B: Regression Coefficient,
CI: Confidence Interval.
The Significant P Values Expressed With Bold Style.

		B	95% CI	P
HCQ DAILY DOSAGE	Subfoveal	1.004	-2.016/4.161	0.245
	Nasal 500	-0.976	-3.417/1.854	0.239
	Nasal 1500	-0.667	-2.166/1.565	0.486
	Temporal 500	2.104	-1.019/4.754	0.313
	Temporal 1500	-1.116	-3.954/1.617	0.219
HCQ CUMULATIVE DOSE	Subfoveal	1.105	0.059/5.423	0.004
	Nasal 500	0.998	0.109/4.329	0.002
	Nasal 1500	0.990	0.036/5.002	0.006
	Temporal 500	1.214	0.213/5.879	<0.001
	Temporal 1500	1.101	0.198/5.456	<0.001

Discussion

The goal of the study was to investigate the effect of HCQ on CT. We found out that CT was thicker at all measured regions in the patients using HCQ compared to healthy controls and thicker CT found to be associated with cumulative HCQ dose. The thickening of the CT could be related to accumulation of HCQ in choroidal tissue as well as RPE.

The degree of the impairment caused by HCQ has not been cleared. Although a few statements presented inner and outer retinal defects related to chloroquine use, some statements exposed that the interior retina is comparatively unbroken in eyes with HCQ retinopathy (6,10). The choroid, however, has not been talked as a mutilation site of HCQ, although choroid, RPE and photoreceptor cells are closely related with each other in several retinal diseases. A disease with impairment at the level of RPE and photoreceptor cells cannot be thought of without choroidal alterations. Ahn et al (11) reported the CT of the patients with HCQ retinopathy was significantly thinner than those without retinopathy. They also investigated the possible reasons for this thinning and found out that the major reason for this thinning is HCQ retinopathy itself rather than the cumulative dose and the duration of the HCQ use. Their findings are harmonious with ours. We hypothesize that the choroid thickens with the use of HCQ, however after the retinopathy occurs, the choroid starts to get thinner, therefore these findings could be useful in terms of the early diagnosis of the HCQ retinopathy.

As HCQ retinopathy is irreparable, appropriate monitoring for retinal toxicity is essential to avoid irreversible visual loss in patients using this drug for rheumatic or inflammatory sicknesses. The American Academy of Ophthalmology recently suggested screening recommendations for HCQ retinopathy (1,2,7). These suggestions assert that the objective of monitoring for HCQ retinopathy is not to discontinue the respected drug when there are uncertain irregularities, but to identify conclusive marks of toxicity at an initial enough period to avoid vision loss (1). However, when patients taking HCQ progress retinal pigmentary alteration or even outer retinal difference on OCT scans, it signifies that the outer retinal layers have already been permanently impaired. Consequently, the early recognition of HCQ retinopathy lessens the functional defect. Nevertheless, in clinical practice, the revealing of early retinopathy can be very difficult in cases of unclear SD-OCT findings (12) and normal-appearing FAF, for which multifocal electroretinogram and visual field examinations (12,13) might be useful. Despite our outcomes regarding the association between HCQ usage and choroidal thickening, the clinical application of choroidal assessment for the detection of HCQ retinopathy is uncertain; so, advanced studies are necessary to verify its practicality. Also, clarifications of choroidal thickening necessitate concern of the factors affecting CT, such as topographical change of the thickness, refractive error, diurnal difference, and age (5,14-17). However, CT evaluation in the patients with HCQ use seems promising in terms of the early detection of the

retinopathy with opposite findings which is thickening with the use of HCQ but thinning with the retinopathy. Therefore, with a regular follow-up, the alterations in the CT could help us to detect early retinopathy. However, it is impossible for this study to draw such a definite conclusion because of its retrospective design. To support this theory that CT could be useful in terms of detection of early HCQ retinopathy, prospective longitudinal follows studies are needed.

It is known that the choriocapillaris provides for the outer retinal layers, with the RPE and photoreceptor levels. Thus, it is believable to doubt the choroidal association in the growth of HCQ retinopathy. The choroid can be simply open to systemic medications due to its rich vasculature. As melanin may play a contributing role in the progress of HCQ retinopathy by concentrating the drug and thus extending toxic results, (1) the choroid, which is rich in melanin pigment, may be susceptible to HCQ toxicity. But, no conclusions regarding a cause-effect affiliation between choroidal thickening and use of HCQ can be drawn from our outcomes, as this was a cross-sectional study only showing a connection among choroidal thickening and HCQ use.

There are several limitations of the present study. The first limitation is the nature of the methodology which is retrospective and cross-sectional, therefore, no definite conclusion could be done and because of the retrospective design, no subject had multifocal electroretinogram or fundus autofluorescent imaging and therefore, some HCQ retinopathy patients who were at the early phase could be missed. The second limitation is the rather small sample size. Prospective studies with a larger sample size could give more information about the effect of HCQ use on CT. We did not investigate the effects of systemic diseases, in which the patients use HCQ for treatment. There are several studies that showed proof of the alterations on CT in different type of diseases, so it is another limitation of this study (18-20).

In conclusion, HCQ use found to be effective on CT, and thicker CT is associated with the cumulative dose of the HCQ that the patients used. Thickening in submacular choroid could be due to the accumulation of these drugs in the choroidal melanocytes and reactions from the surrounding tissues. Further studies investigating CT in patients with retinal toxicity would reveal if subsequent atrophy or thinning comes after.

Yazarlık Katkısı: Fikir/Hipotez: HY, DA, AHD, FMM Tasarım: HY, DA, MK, GÖ, AHD, FMM Veri toplama/Veri işleme: MK, GÖ Veri analizi: MK Makalenin hazırlanması: HY Makalenin kontrolü: AHD, FMM

Etik Kurul Onayı: Hitit Üniversitesi Etik Kurul Komitesi'nden (2020/343 karar no'lu). Çalışma Helsinki Deklarasyonu'na uygun olarak yürütülmüştür.

Hasta Onayı: Gerekli değildir.

Hakem Değerlendirmesi: İlgili alan editörü tarafından atanan iki farklı kurumda çalışan bağımsız hakemler tarafından değerlendirilmiştir.

Çıkar Çatışması: Yazarlar tarafından çıkar çatışması bildirilmemiştir.

Finansal Destek: Yazarlar tarafından finansal destek almadıkları bildirilmiştir.

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