Effects of COVID 19 and Short-term Hydroxychloroquine Usage on Retina and Choroid

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ABSTRACT

Purpose: This study aims to assess the effects of coronavirus disease 2019 (COVID-19) and short-term hydroxychloroquine (HCQ) usage on retina and choroid in COVID-19 patients.

Materials and Methods: This is a cross-sectional, observational, comparative study. Group 1 consisted of 36 healthy individuals, and Group 2 consisted of 31 subjects with COVID-19 and short-term hydroxychloroquine usage. The subfoveal choroidal thickness, retinal nerve fiber layer (RNFL) thickness, and macular thickness were evaluated utilizing spectral-domain OCT after a detailed ophthalmologic examination.

Results: The mean age of the Group 1 was 29.47±7.6 years, and the mean age of the Group 2 was 30.45±7.2 years. In Group 1, 44.4% of the patients were female, while in Group 2, 61.2% of the patients were female. There was no statistically significant difference in age, gender distribution, smoking status, intraocular pressure, and spherical equivalent values between the groups. The subfoveal choroidal thicknesses of the right and left eyes were found lower in Group 1 than Group 2; however, these differences were not statistically significant [p=0.22 (right), p=0.11 (left)]. Furthermore, RNFL thicknesses and macular thicknesses were similar in both groups.

Conclusion: The COVID-19 and short-term HCQ usage had no significant negative effects on retina and choroid.

Keywords: Choroid, COVID-19, Hydroxychloroquine, Retina.

INTRODUCTION

The coronavirus disease 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), first appeared in Wuhan, China. Dr. Wenliang Li, an ophthalmologist, first noticed COVID-19. COVID-19 spread rapidly to almost all countries around the world. The World Health Organization initially announced a Public Health Emergency of International Concern and officially confirmed the COVID-19 as a pandemic outbreak in March 2020.[1] Since then, it has deeply affected life worldwide and caused the deaths of millions of people.

The SARS-CoV-2 mainly uses angiotensin-converting enzyme 2 (ACE-2) as the viral entry receptor into cells.[2] Previous studies demonstrated that the ACE-2 receptor presents some human ocular tissue such as conjunctiva and retina.[3, 4] Furthermore, the presence of ocular findings associated with COVID-19 and the detection of viruses in the conjunctival swab and retina also support the importance of the eye.[5-9] SARS-CoV-2 has been shown in studies to impact the retina and choroid via direct entrance or an indirect inflammatory response.[10, 11] Retinal manifestations are mainly caused by microvascular abnormalities. The most common retinal findings are cotton wool spots, intraretinal hemorrhages, paracentral acute middle maculopathy, acute macular neuroretinopathy, or retinal vein occlusions.[10, 12, 13]

The SARS-CoV-2 is highly contagious, causes respiratory distress syndrome, and can lead to death, especially in at-risk patients with pre-existing and concomitant diseases.[14] Although many treatment options have been recommended for this potentially fatal disease, to date, no specific therapy has been identified to manage COVID-19. However, besides antiviral drugs, hydroxychloroquine (HCQ) has been used to treat SARS-CoV-2 infection in some countries in the world.[15] This may be because HCQ has been postulated to decrease viral replication in other coronavirus infections.[16] Although HCQ lost its initial

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popularity with recent studies, it is still used in some countries. HCQ is well known to ophthalmologists for its retinal toxicity after long-term use for systemic lupus erythematosus and other rheumatoid diseases.[17] Although HCQ is taken for a short time in COVID-19, its recognized retinal toxicity has raised some safety cares, particularly regarding the higher dosage used for COVID-19 patients than their recommended relatively safe daily dose.[18, 19]

While there are a restricted number of studies about the effects of COVID-19 on the retina and the choroid.[9, 13], best our knowledge, there are no clinical researches on the impacts of short-term HCQ usage on the retina and choroid. In this study, we aim to evaluate the effects of COVID-19 and short-term HCQ usage on retina and choroid in COVID-19 patients. For this purpose, retinal nerve fiber layer (RNFL), macular thickness, thickness, and subfoveal choroidal thickness were measured with spectral-domain optical coherence tomography (SD-OCT) in all subjects.

MATERIALS AND METHODS

In this prospective study, the macular, RNFL and subfoveal choroidal thicknesses of patients with COVID-19 and short-term HCQ usage was measured and compared with the control group. Group 1 consisted of 36 healthy individuals and group 2 consisted of 31 patients with COVID-19 and short-term HCQ usage. All cases in Group 2 were selected from patients whose COVID-19 Polymerase Chain Reaction (PCR) tests were done at COVID-19 at the Emergency Department for COVID-19 symptoms. To avoid the risk of COVID-19 transmission, patients diagnosed with COVID-19 about two months ago were included in Group 2. Patients with COVID-19 who did not need hospitalization and had mild symptoms were mainly treated with HCQ sulfate 200 mg (Korokin, Kocak Farma, Istanbul, Turkey) orally twice a day for five days, according to the ministry of health guide. Informed consent was received from all subjects, and the Helsinki Declaration was followed throughout the study. Ethics committee approval was received from the Malatya Clinical Research ethics committee (protocol code: 2020/122)

The same ophthalmologist performed a complete ophthalmologic examination. Visual acuities were recorded separately for both eyes, according to Snellen charts. Anterior segment examination, intraocular pressure measurements, and detailed fundus examination with a +90 D non-contact lens were performed by slit-lamp examination. Finally, macular, RNFL and subfoveal choroidal thicknesses of both eyes were measured by SC-OCT.

Inclusion criteria were described as age between 18-50, spherical equivalent < ± 3.0 diopter, no prior ocular surgery history, no other ocular and neurological diseases, best-corrected visual acuity of 20/20 for both eyes, no associated systemic disease for both groups and treated with HCQ sulfate 200 mg orally twice a day for five days for Group 2.

Macular, RNFL and subfoveal choroidal thicknesses measurements: All measurements were performed with SD-OCT (RS-3000 Advance, NIDEK, Japan). All OCT images were performed independently by an experienced operator, and the operator was blinded to the patients' information. Of the measurements, the best signal strength was recorded for analysis, but not less than 7. RNFL thickness was measured along a 6x6 millimeter square centered on the optic disk. Mean RNFL thickness was measured and analyzed in the statistical interpretation. Macular thickness determinations were obtained in the nine areas described in the Early Treatment Diabetic Retinopathy Study (ETDRS) using the SD-OCT device's software.[20] Subfoveal choroidal thickness was measured with EDI-OCT scanning. Choroidal thickness was measured between the outer border of the retinal pigment epithelial layer and the manually marked sclero-choroidal interface area.

Statistical analysis: IBM SPSS Statistics for Windows, Version 22.0 (IBM Corp., Armonk, NY, USA) was used to analyze our research data. The power analysis determined that at least twenty five volunteers were required for each group. Descriptive statistical data for categorical variables were summarized as numbers, and statistical data for continuous variables were informed as mean and standard deviation or median and minimum-maximum values. The Shapiro-Wilk test examined the suitability of continuous variables to normal distribution. In order to investigate the differences between the two groups, student t-test, and Mann Whitney U test were used. The Chi-square test was used to evaluate qualitative data. The confidence level was reported as 95% in the analyses. A p-value of less than or equal to 0.05 was recognized as statistically significant.

RESULTS

A total of 67 subjects (36 Group 1 and 31 Group 2) were included in the study. Group 1 had a mean age of 29.47±7.6 years, whereas Group 2 had a mean age of 30.45±7.2 years. There was no statistically significant difference in terms of age (p=0.51), gender distribution (p=0.25) and smoking status (p=0.06) values between the groups. Also there was no statistically significant difference in terms of intraocular pressure [p=0.33 (right), p=0.64 (left)] and spherical equivalent [p=0.59 (right), p=0.23 (left)] values between the groups (Table 1).

The average time between COVID-19 diagnosis and eye

Table 1. *Demographic features of the groups.*				
		Group 1	**Group 2**	**P value**
Age (year) (mean±SD)		29.47 ±7.6	30.45±7.2	0.51[a]
Gender (n)	Female	16	19	0.25[b]
Smoking status (p-y) (median) (min/max)	Male	20 0(0/20)	12 0(0/15)	0.06[a]
SE (median) (min/max)	Right eye	-0.50 (-2.00/+1.75)	-0.50 (-3.00/+2.00)	0.59[a]
	Left eye	-0.75 (-2.00/+2.00)	-0.50 (-3.00/+2.50)	0.23[a]
IOP (mean±SD) **(mm Hg)**	Right eye Left eye	14.31±2.2 14.69±2.5	14.87±2.5 14.97±2.3	0.33[c] 0.64[c]
SD: Standard deviation, p-y: Pack-year, SE: Spherical equivalent, IOP: Intraocular pressure, [a]Mann-Whitney U test, [b]Chi-square test, [c]Student t-test				

examination was 63.29±5.7 days. While three patients had no symptoms associated with COVID-19, 28 patients had symptoms. The most frequent symptoms in patients were fever, fatigue, headache, dry cough, and arthralgia. None of the patients had any eye-related symptoms. The patients' symptoms are as shown in Figure 1.

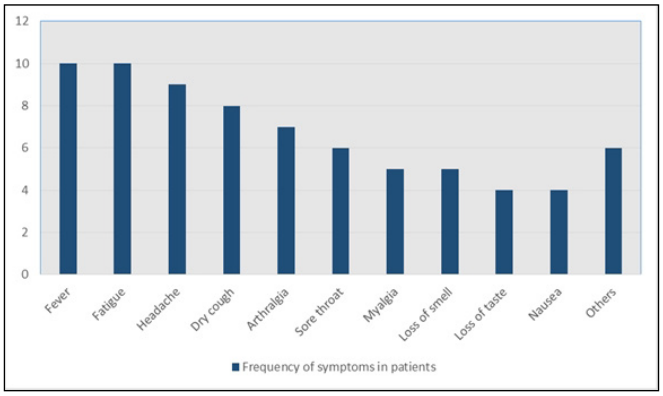

Figure 1. *The frequency of symptoms in COVID-19 patients.*

Fundus examination of all patients with a +90 D non-contact lens was normal. The macular, RNFL and subfoveal choroidal thicknesses measurements were performed with SD-OCT. The mean of subfoveal choroidal thicknesses were 324.0±57.6 µm in the right eye and 324.06±59.6 µm in the left eye in Group 1, while it was 341.26±34.7 µm in the right eye and 353.87±44.2 µm in the left eye in Group 2. It was observed that subfoveal choroidal thicknesses of the right and left eyes were lower in Group 1 than Group 2; however, these differences were not statistically significant. Furthermore, RNFL thicknesses in both eyes were similar in groups (Table 2). Nine areas of ETDRS were used for both eyes to evaluate macular thickness. In Group 1, macular thickness was similar in all areas in both eyes compared to Group 2 (Table 3).

DISCUSSION

Studies are showing that COVID-19 may have effects on the retina. In contrast, in this current study, it was seen that the macular thickness and RNFL thickness were similar between COVID-19 patients and the control group. When the subfoveal choroidal thickness was compared, it was observed that there was an increase in subfoveal choroidal thickness in COVID-19 patients compared to the control subjects. However, this increase was not statistically significant.

Senanayake et al. investigated ACE-2 receptors in the tissues of the posterior segment of the eye in their study on cadaveric eyes.[3] They detected that ACE-2 receptor density was highest in the neural retina, about half of that in the retinal pigment epithelium and choroid, and less in the optic nerve and the lowest in the ciliary body-iris complex. Considering this expression of the ACE-2 receptor, it is

Table 2. *Mean choroidal and RNFL thicknesses of right and left eyes of the groups.*				
		Group 1	**Group 2**	**P value**
Choroid (µm) (mean±SD	Right eye	324.0±57.6	341.26±34.7	0.22[a]
RNFL (µm) (mean±SD	Left eye	324.06±59.6	353.87±44.2	0.11[a]
	Right eye	114.31±10.5	113.52±11.8	0.83[a]
	Left eye	113.0±10.2	113.26±12.1	0.90[a]
RNFL: Retinal nerve fiber layer, SD: Standard deviation, [a]Mann-Whitney U test				

Table 3. *Mean macular thickness of the right and left eyes of the groups according to ETDRS areas.*

ETDRS areas of right eye		Group 1 Mean±SD (µm)	Group 2 Mean±SD (µm)	P value
Central macula	Right eye	264.72±22.2	262.61±21.5	0.91[a]
	Left eye	267.33±26.4	260.58±18.4	0.59[b]
Superior-inner	Right eye	344.0±23.7	342.9±19.5	0.56[a]
	Left eye	346.61±17.5	345.68±17.1	0.82[a]
Temporal-inner	Right eye	332.83±14.2	330.29±15.3	0.48[b]
	Left eye	332.61±14.6	331.52±17.0	0.97[b]
Inferior-inner	Right eye	341.00±22.9	337.19±19.6	0.25[a]
	Left eye	339.97±20.9	340.25±17.8	0.80[b]
Nasal-inner	Right eye	347.72±15.3	346.55±16.1	0.76[b]
	Left eye	346.50±16.7	344.06±16.4	0.55[a]
Superior-outer	Right eye	309.78±14.7	312.74±13.4	0.39[b]
	Left eye	311.19±14.8	309.68±13.0	0.66[a]
Temporal-outer	Right eye	294.31±12.3	294.19±15.7	0.97[b]
	Left eye	294.36±13.2	293.06±16.2	0.72[a]
Inferior-outer	Right eye	300.61±16.2	301.71±14.9	0.77[b]
	Left eye	301.00±16.7	299.48±14.9	0.46[b]
Nasal-outer	Right eye	325.42±14.3	323.26±12.7	0.52[b]
	Left eye	325.97±14.2	323.81±15.2	0.55[a]

ETDRS:Early treatment diabetic retinopathy study, [a]Mann-Whitney U test, [b]Student t-test

likely that SARS-CoV-2 also affects the retina. Casagrande et al. examined retinal biopsies of 14 patients who died with confirmed COVID-19, and they detected COVID-19 viral RNA in retinal biopsies of 3 patients.[8]

Marinho et al. examined the retinas of 12 confirmed COVID-19 patients with OCT. All patients displayed hyperreflective lesions at the ganglion cell and inner plexiform layers more prominently at the papillomacular bundle in both eyes.[9] Also, four patients had subtle cotton wool spots and microhemorrhages adjacent to the retinal arcade. Additionally, they reported that patients did not have any abnormal findings in OCT-angiography and ganglion cell complex analysis. No abnormal lesions were observed in SD-OCT sections and fundus examination of COVID-19 patients in our study. This difference may result from the younger age and the longer duration between the diagnosis of COVID-19 and the SD-OCT examination in our patients. Direct measurements of the ganglion cell complex were not performed in our study. Instead, macular thickness and RNFL thickness measurements were made. Although they are not the same, they are structures that are intertwined. Similar to the Marinho et al. study, they appeared to be normal in our study.

Landecho et al. also reported cotton wools spots in 6 (22%) of 27 COVID-19 patients, all hospitalized due to bilateral pneumonia, and suggested that this was associated with COVID-19 retinal microangiopathy.[21] Invernizzi et al. evaluated the retina's changes and its vasculatures and possible correlations with clinical parameters in a controlled study in which 54 COVID-19 patients were included.[12] They reported that hemorrhages (9,25%), cotton wool spots (7,4%), dilated veins (27,7%), tortuous vessels (12,9%) in the retinas of COVID-19 patients. The high retinal findings in these studies, according to our study, may result from the higher age of the patients, the more severe disease, and the presence of comorbid diseases.

Invernizzi et al. also found average artery diameter and average veins diameter were larger in COVID-19 patients than unexposed subjects.[12] Additionally, in COVID-19 patients, the average vein diameter was negatively correlated with symptoms onset and positively correlated with disease severity. Microangiopathy and/or hypoxia caused by COVID-19 may have resulted in this vessel dilatation.[21-23] Similarly, possible vascular dilatation in the choroidal layer due to the vessels' richness in the choroidal layer may increase the choroid's thickness. The increase in choroidal thickness in COVID-19 patients in our study may have resulted from this vascular dilatation.

A letter to the editor in the literature evaluating RNFL thickness in COVID-19 patients. [24] This publication

evaluated the RNFL thickness of five COVID-19 patients before and after diagnosis of COVID-19 and reported a 4.3 μm increase in mean RNFL thickness, but statistical significance was not mentioned. The author proposed that this increase may be due to virus-associated inflammation or hypoxia. Considering that the mean age of the patients is 65.4 years, no information about the presence of pneumonia, hospitalization, and comorbid diseases are important limitations of this letter. In our study, RNFL thickness was almost the same in both eyes of groups.

Savastano et al. investigated peripapillary vascular impairment in post-SARS-CoV-2 patients in their study.[25] They also evaluated RNFL thickness, subfoveal choroidal thickness, central foveal thickness similarly to our research. In the study of Savastano et al., COVID-19 patients were more heterogeneous than our study in terms of age, comorbidity, medications, and disease severity. Additionally, just 68.8% of COVID 19 patients used HCQ. Similar to our study, in this study, there was no statistical difference between the COVID-19 patients and the control subject in terms of RNFL thickness, subfoveal choroidal thickness, and central foveal thickness.

Preclinical studies demonstrated that HCQ is melanotropic drugs that bind to the melanin in the retinal pigmented epithelium; however, it has not clearly understood the pathogenic mechanism thought to occur primarily in the neural retina.[18, 26] The early phases of HCQ retinal toxicity are frequently asymptomatic, with no changes in visual acuity.[18] Patients with late phases of the disease may have diminished visual acuity and peripheral vision, as well as the formation of paracentral scotomas and changes in night vision.[27] In HCQ toxicity, a bull's-eye appearance and usually irreversible vision loss can be observed due to perifoveal retinal pigment epithelial atrophy.[28] Considering that this iatrogenic retinopathy is associated with high-dose, long-term treatment, and concomitant renal disease, possible retinal toxicity in COVID-19 patients in our study could occur due to the use of high-dose HCQ in the short term.

The American Academy of Ophthalmology has suggested that the maximum daily dose for HCQ be ≤5.0 mg/kg.[27] Similarly, the British Royal College of Ophthalmologists has stated that a daily dose of HCQ less than 5 mg/kg/day for less than five years is relatively safe for retinal toxicity.[29] All COVID-19 patients in our study received 400 mg of HCQ per day; this is higher than the recommended dose for any patient who weighs less than 80 kg.[30] Although we did not regularly note the patients' body weight, which is a limitation of our study, our patients' body weights varied between 60-90 kg. In particular, the short duration of HCQ usage (5 days), the amount of taken dose relatively close to the recommended dose, the younger age of the patients, and the absence of comorbid retinal disease may have contributed to the lack of retinal alterations. Moreover, the mildness of the disease in the COVID-19 patients in our study may have prevented an additive effect on the negative effect of HCQ on the retina.

In conclusion, COVID-19 and short-term HCQ usage had no significant negative effects on retina and choroid in healthy young patients except COVID-19. However, in light of previous studies, COVID-19 and short-term HCQ usage may negatively impact the retina and choroid in patients with advanced age, having comorbid diseases, and severe COVID-19. We believe that more valuable results can be obtained with prospective controlled studies in these patient groups.

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