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Ocular safety of hydroxychloroquine when used as prophylaxis against COVID-19 in healthcare workers at a tertiary care center in India

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ABSTRACT

BACKGROUND: The aim was to correlate hydroxychloroquine's dose and duration and its effect on colour vision, contrast sensitivity, retinal nerve fiber layer (RNFL) and macula assessed by optical coherence tomography (OCT) and to comment on the ocular effects of a short-term high-dose course of hydroxychloroquine in healthcare workers. A cross-sectional observational study was done in a large 650-bed tertiary centre managing around 2500 COVID-19 patients. The healthcare workers rendering the care were administered hydroxychloroquine optionally as a prophylaxis against Sars-Cov-2 infection. The healthcare workers who used hydroxychloroquine prophylaxis were enrolled in this study. The dose and duration of hydroxychloroquine were noted.

MATERIAL AND METHODS: Ethical clearance was sought and the enrolled individuals underwent a detailed ophthalmic examination. The OCT of RNFL thickness with ganglion cell layer (GCL) and OCT macula was assessed. The dose of hydroxychloroquine received and its effects on colour vision, contrast sensitivity, OCT RNFL thickness, and OCT macula were correlated. Statistical analysis was performed with SPSS software for Windows, version 18. The correlation between the exposure time, cumulative dose, and SD-OCT parameters was evaluated using Pearson's correlation coefficient. p-values < 0.05 were considered statistically significant.

RESULTS: Average macular thickness and RNFL thickness in all quadrants did not significantly correlate ($p > 0.001$) with a cumulative dose of hydroxychloroquine and the duration of hydroxychloroquine use.

CONCLUSIONS: Our study concludes that no ocular adverse effects are noted with the high-dose short-term use of hydroxychloroquine for COVID-19 prophylaxis in contrast to the long-term use of hydroxychloroquine for several systemic conditions.

KEY WORDS: hydroxychloroquine; COVID-19 prophylaxis; hydroxychloroquine retinopathy

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INTRODUCTION

Hydroxychloroquine is an anti-malarial medication that has, in recent times, been utilized as a treatment for a variety of autoimmune diseases, such as rheumatoid arthritis and systemic lupus erythematosus. In the current pandemic, with few studies indicating intriguing possibilities about the drug's potential as a preventive medication against Sars-CoV-2 infection, the usage of the drug showed a drastic positive shift. The anti-inflammatory effects of hydroxychloroquine are well established, and they range from interference with lysosomal functioning, antigen presentation, inhibition of phospholipase A2, inhibition of T

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and B cell receptors, and decreasing cytokine production by macrophages such as interleukins (IL): IL-1 and IL-6 [1]. This has proven to be effective in treating various autoimmune conditions and has been the basis for its use in effective management. The anti-inflammatory properties addressing the cytokine storm, an immune response observed in Sars-CoV-2 infection, predominantly mediated by tumor necrosis factor alpha (TNF-α) and IL-6, are addressed by the anti-inflammatory effects of hydroxychloroquine. In addition to this, hydroxychloroquine causes impairment of glycosylation of angiotensin-converting enzyme-2 receptor, decreasing viral-receptor affinity, reducing the initiation of the infection, and rendering the cells refractory to viral entry [2].

The worldwide effects of the COVID-19 pandemic have been unparalleled and prompted the scientific community to consider all possible solutions as prophylaxis and a cure. The safe dosage of hydroxychloroquine was concluded to be 6–6.5 mg/kg per day, based on several trials , which is the required concentration in the tissues needed to inhibit SARS-CoV-2 infection [3].

For many years, it has been known that hydroxychloroquine and its analogue, chloroquine, have numerous side effects, predominantly retinal toxicity. Early stages of hydroxychloroquine retinopathy can be asymptomatic with preservation of visual acuity or have subtle changes in night vision, diminished colour vision, or a paracentral scotoma [4]. In advanced hydroxychloroquine retinopathy, significant deterioration of visual acuity, peripheral vision, and night vision accompanied by classic "bull's eye maculopathy," which is a perifoveal ring of retinal pigment epithelium (RPE) atrophy sparing the fovea [4]. Retinal toxicity secondary to hydroxychloroquine is irreversible. It can continue to progress following cessation of therapy [5]. The objective changes typically preceding a patient's complaint of vision loss advocate prompt screening and serial monitoring, with the utilization of imaging modalities as of paramount importance for early detection.

High-resolution cross-sectional images of the retina using spectral domain optical coherence tomography (SD-OCT) may detect disruption, or complete loss, of the outer nuclear layer, external limiting membrane, inner/outer segment junction, and RPE in the parafoveal region in hydroxychloroquine retinopathy [6]. In the study by Pasadhika et al., thinning of the perifoveal inner retinal layer, especially the inner plexiform and ganglion cell layer (GCL), was also observed by SD-OCT in hydroxychloroquine treated patients in the absence of clinically evident retinal toxicity [7]. Thus, prospective evaluation of retinal changes using SD-OCT during hydroxychloroquine treatment may be warranted to detect structural changes early enough to avoid irreversible retinal damage. Once hydroxychloroquine toxicity is detected/suspected, the drug should be stopped immediately.

Literature has proved over the years the above-mentioned side effects of long-term use of hydroxychloroquine. During COVID-19 pandemic, as a prophylaxis for Sars-CoV-2 infection, the government of India initiated a nationwide measure of the use of hydroxychloroquine in the healthcare professionals involved in the COVID-19 hospital duties. The hydroxychloroquine used in this program was 4–5 times the recommended dose required for treating various autoimmune diseases, such as rheumatoid arthritis and systemic lupus erythematosus, and for a short term. The use of hydroxychloroquine in high doses and short term and its effect on ocular tissues hasn't been studied in depth. In this study, we try to assess the ocular side effects of high-dose and short-term administration of hydroxychloroquine.

MATERIAL AND METHODS

A cross-sectional observational study was done in a tertiary centre managing COVID-19 patients after the approval from the ethics committee (Registration number is ECR/215/inst/KA/2013/RR-16). The facility was a large 650-bed hospital, where the manpower requirement to manage the care of around 25,000 patients during the peaks of the pandemic was enormous. The healthcare workers were administered hydroxychloroquine optionally as a prophylaxis against COVID-19, as they were either posted to perform COVID-19 duties or were at risk of being exposed to Sars-CoV-2-positive patients during non-COVID-19 duty. The healthcare workers who used hydroxychloroquine prophylaxis were enrolled in this study. The usual dose of hydroxychloroquine is 400 mg twice a day (BD, *bis in die*) as 1st dose followed by 400 mg once a day (OD, *omnie die*)/week subsequently. However, the dose and the duration of hydroxychloroquine taken varied. Hence, the details on the dose of the hydroxychloroquine received, the duration for which hydroxychloroquine was taken, and if hydroxychloroquine was stopped in be-

tween the course of prophylaxis with the reason for the same was noted. Any pre-existing ocular morbidity was also noted. Individuals with a history of use of hydroxychloroquine for other conditions like systemic lupus erythematosus, rheumatoid arthritis, etc., and individuals with pre-existing glaucomatous changes, diabetic retinopathy and other forms of retinopathy were excluded. The enrolled individuals then underwent a detailed ophthalmic examination, including visual acuity using Snellen's chart, best-corrected visual acuity, color vision, contrast sensitivity testing, slit-lamp examination of the anterior segment, retinal examination with slit lamp biomicroscope and dilated fundoscopy with 90D lens and Indirect ophthalmoscope. The retinal nerve fiber layer (RNFL) thickness with GCL was assessed using TOPCON 3D OCT-1 Maestro, SD-OCT with OCT-RNFL comprehensive protocol. We correlated the dose of the hydroxychloroquine received and its effects on color vision, contrast sensitivity and OCT-RNFL thickness. In addition, the interval between the last dose of hydroxychloroquine taken and the ocular examination was noted.

Statistical analysis was performed with SPSS software for Windows, version 18. The distributions of continuous variables were determined by a Kolmogorov-Smirnov test. The mean differences among groups were analyzed using a Student's t-test. The correlation between the exposure time, cumulative dose, and SD-OCT parameters was evaluated using Pearson's correlation coefficient. The data are expressed as the mean ± standard deviation for the continuous variables. p-values < 0.05 were considered statistically significant.

RESULTS

A total of 61 healthcare workers who used hydroxychloroquine were analysed in the study. The participants' mean age was 45.0 ± 13.16 years. Amongst the study participants, 56% were females and 44% were males. The demographic details of the enrolled individuals are specified in Table 1.

Table 1. Demographic details

Parameters	
Age	45 ± 3 years
Females	34 years
Males	27 years
IOP (mm Hg)	16.09 ± 2.44
CDR	0.33 ± 0.12

IOP — intraocular pressure; CDR — cup-to-disc ratio

The best-corrected visual acuity assessed by Snellen's chart in all the enrolled individuals showed a mean distance vision of 6/6, and the mean near vision using Jaeger's chart was N6. Colour vision assessed by Ishihara chart in all patients was normal with enrolled individuals reading 21/21 plates. The contrast sensitivity was evaluated using Pelli Robson's chart, and all the enrolled individuals had normal contrast sensitivity. The anterior segment evaluation in all the individuals showed clear cornea, normal AC depth with Van Herick's grade 4, briskly reacting pupil, and a clear lens. Dilated fundus examination showed clear media, cup-to-disc ratio (CDR) 0.3:1, well defined margins, normal blood vessels, normal background, macula showed sharp foveal reflex in all the enrolled individuals except 2 patients, where the CDR was 0.4:1 , with well-defined margins, healthy neuroretinal rim thinning (NRR). The mean cumulative dose of hydroxychloroquine exposure was 7095.1 mg, and the mean duration of hydroxychloroquine use was 4.5 months.

OCT-macula and OCT-RNFL of both eyes were performed. Average macular and central macular thickness was obtained from OCT macula of both eyes. The mean average macular thickness in the right eye was 271.2 ± 15.1 microns, whereas the mean average macular thickness in the left eye was 268.1 ± 24.6 microns. The mean central macular thickness in the right eye was 178.8 ± 16.1 microns, whereas the mean central macular thickness in the left eye was 177.7 ± 16.6 microns, as described in Table 2.

Table 2. Mean macular thickness

Macula thickness	Mean [microns]	SD [microns]
Average thickness macula — right eye	271.3115	15.12232
Central thickness — right eye	178.9836	16.10227
Average thickness macula —left eye	268.0328	24.56147
Central thickness — left eye	177.7377	16.59106

SD — standard deviation

Table 3. Mean retinal nerve fibre layer (RNFL) thickness		
RNFL thickness — quadrants	**Mean [microns]**	**SD [microns]**
Average — right eye	109.2295	10.99605
Superior — right eye	137.1475	15.88903
Inferior — right eye	132.3607	23.48974
Nasal — right eye	98.01639	26.6955
Temporal — right eye	71.7541	16.72987
Average — left eye	106.5738	15.04046
Superior — left eye	136.0984	23.58792
Inferior — left eye	126.918	28.98867
Nasal – left eye	89.44262	31.31694
Temporal – left eye	72.72131	15.96572

SD — standard deviation

The average RNFL thickness in the right eye was 109.2 ± 10.9 microns, whereas the mean average RNFL thickness in the left eye was 106.5 ± 15.1 microns. The mean values of the RNFL thickness in each quadrant are described in Table 3.

The mean RNFL thickness in both eyes of the enrolled individuals was within the normal range compared to the age and sex-matched population-based nomogram. The average normal RNFL thickness is 113.46 ± 10.90 microns [8]. The mean GCL thickness in the right eye showed to be maximum in the superonasal quadrant (75.9 ± 8.7 microns) and the least in the inferior quadrant (67.9 ± 6.1 microns). Similarly, the mean GCL thickness in the left eye was maximum in the inferonasal quadrant (74.1 ± 7.8 microns) and the least in the inferior quadrant (69.2 ± 4.8 microns), as described in Table 4.

The parametric correlation analysis using the Pearson correlation showed that average macular thickness (Tab. 5), average RNFL thickness, superior, inferior, nasal, temporal quadrant thickness did not significantly correlate ($p > 0.001$) with a cumulative dose of hydroxychloroquine and the duration of hydroxychloroquine use (Tab. 6). The correlation between the GCL thickness in all the quadrants of the retina did not correlate significantly with the cumulative dose of hydroxychloroquine and the duration of hydroxychloroquine use ($p > 0.001$) as described in Table 7.

Table 4. Mean ganglion cell layer (GCL) thickness		
GCL	**Mean [microns]**	**SD [microns]**
Right eye quadrants		
Superior	70.86885	6.443279
Supero nasal	75.98361	8.789182
Infero nasal	74.59016	8.401145
Inferior	67.98361	6.146793
Infero temporal	71.27869	6.319629
Supero temporal	69.72131	7.106643
Superior GCL++	106.6721	10.28546
Supero nasal GCL++	116.0492	12.88336
Infero nasal GCL++	114.4426	12.6498
Inferior GCL++	105.0656	14.32581
Infero temporal GCL++	95.54098	7.856152
Supero temporal GCL ++	92.08197	8.914959

Table 4. Mean ganglion cell layer (GCL) thickness

GCL	Mean [microns]	SD [microns]
Left eye Quadrants		
Superior	70.36066	7.650779
Supero nasal	73.57377	8.720587
Infero nasal	74.03279	7.861228
Inferior	69.21311	4.878916
Infero temporal	72.57377	5.990156
Supero temporal	71.44262	7.102874
Superior GCL ++	104.7869	9.776016
Supero nasal GCL ++	114.2787	17.61073
Infero nasal GCL ++	115.4098	14.6985
Inferior GCL ++	104.3934	13.87357
Infero temporal GCL ++	96.29508	7.521844
Supero temporal GCL ++	94.80328	15.55616

SD — standard deviation; GCL++ — ganglion cell layer + retinal nerve fibre layer (RNFL) + inner plexiform layer

Table 5. Dose of hydroxychloroquine and correlation with optical coherence tomography (OCT) of macula

OCT parameter	Correlation coefficient h hydroxychloroquine dose (p-value)
Average thickness macula Right eye	0.62
Central thickness Right eye	0.16
Average thickness macula Left eye	0.89
Central thickness Left eye	0.13

Table 6. Dose of hydroxychloroquine and correlation with retinal nerve fibre layer (RNFL) thickness on optical coherence tomography (OCT)

OCT parameter RNFL Quadrant	Correlation coefficient hydroxychloroquine dose (p-value)
Average right eye	0.30
Superior right eye	0.95
Inferior right eye	0.32
Nasal right eye	0.54
Temporal right eye	0.28
Average left eye	0.73
Superior left eye	0.72
Inferior left eye	0.57
Nasal left eye	0.37
Temporal left eye	0.80

DISCUSSION

Hydroxychloroquine and chloroquine have been used long-term for various conditions like Systemic lupus erythematosus and rheumatoid arthritis. Retinal toxicity of varying degrees has been reported and studied in the literature [9]. Several preclinical studies have been inconclusive about the pathology behind the retinal toxicity secondary to hydroxychloroquine use. Still, it is widely accepted that hydroxychloroquine and chloroquine, being melanotropic drugs, bind to the melanin of retinal pigment epithelium (RPE), and a cascade of reactions set in, leading to lipofuscin accumulation in the RPE. The pathological process of the associated photoreceptor and ganglion cell changes in retinal toxicity due to hydroxychloroquine is not fully understood [10].

Several studies have documented the effect of the long-term hydroxychloroquine use and the chronic use on the RNFL thickness. In the study by Pasadhika et al. [7], significant thinning of peripapillary RNFL was observed in chronic hydroxychloroquine users. In the individuals with RPE changes on fundus examination , diffuse thinning of RNFL and primarily the GCL layer was observed to be affected. Similar to this study, in the study by Lee et al. [11], macular ganglion cell-inner plexiform layer (GC-IPL) thinning was observed in some patients with long-term hydroxychloroquine use on SD-OCT.

Table 7. Dose of hydroxychloroquine and correlation with ganglion cell layer (GCL) thickness on optical coherence tomography (OCT)

OCT parameter GCL	Correlation coefficient with hydroxychloroquine dose (p-value)
Right eye	
Superior GCL	0.71
Supero nasal GCL	0.65
Infero nasal GCL	0.36
Inferior GCL	0.51
Infero temporal GCL	0.54
Supero temporal GCL	0.54
Superior GCL++	0.97
Supero nasal GCL++	0.54
Infero nasal GCL++	0.25
Inferior GCL++	0.92
Infero temporal GCL++	0.61
Supero temporal GCL ++	0.74
Left eye	
Superior GCL	0.41
Supero nasal GCL	0.06
Infero nasal GCL	0.35
Inferior GCL	0.76
Infero temporal GCL	0.59
Supero temporal GCL	0.33
Superior GCL++	0.98
Supero nasal GCL++	0.03
Infero nasal GCL++	0.01
Inferior GCL++	0.85
Infero temporal GCL++	0.35
Supero temporal GCL++	0.57

GCL++ — ganglion cell layer + retinal nerve fiber layer + inner plexiform layer

Marmor and Melles indicate excessive daily dose by weight and the duration of use are the most critical risk factors for the development of hydroxychloroquine toxicity. These authors also demonstrated that the prevalence of retinal toxicity is less than 1% in the first 5 years and less than 2% in the first 10 years of hydroxychloroquine use for individuals prescribed doses of ≤ 5.0 mg/kg [12]. Iatrogenic retinopathy is referred to be associated with a high dosage and long-term treatment period: the American Academy of Ophthalmology (AAO) has recommended a maximum daily dose ≤ 5.0 mg/kg body weight for hydroxychloroquine and ≤ 2.3 mg/kg body weight for chloroquine [13].

The dose used as prophylaxis for health care workers against COVID-19 is 4–5 times higher than those suggested by American Academy of Ophthalmology (AAO) and The Royal College of Ophthalmologists (RCO) [13]. The use of hydroxychloroquine in COVID-19 patients/health care workers can be categorized as high dose but short-term use. As in our study, the usage was for a short term, with a maximum for 6 months. Although several reports conclude the retinal toxicity due to use of hydroxychloroquine, it is attributed to the chronic use of the drug. In contrast to this, in the report by Pasoglu et al, where 2 months of hydroxychloroquine us showed maculopathy changes [14]. However, in our study, there was no significant damage at the macula or RNFL with short term use of hydroxychloroquine. This indicates that maculopathy is caused by multifactorial etiologies and further studies are needed to understand the toxicity mechanisms and also in the subject of short term hydroxychloroquine use for COVID-19, especially in health care individuals and its effect on RNFL thickness.

Considering that the use of hydroxychloroquine in COVID-19 has waned over the past 2 years, the short-term use of hydroxychloroquine in other diseases could be scrutinised. This is because, as seen in our study, the short-term use of hydroxychloroquine, notwithstanding the dose, has a reduced propensity to cause ocular effects. Although there are studies [15] which indicate the short-term dosing of hydroxychloroquine is associated with lower systemic, that is, cardiac, gastrointestinal side effects, there are no conclusive reports on short-term dosing of hydroxychloroquine and ocular manifestation. This warrants further studies on short term hydroxychloroquine use and its ocular manifestation.

CONCLUSIONS

A short-term high dose of hydroxychloroquine shows no ocular side effects, in contrast to the well-studied and clinically advised long-term use of hydroxychloroquine for various medical disorders. Further studies are required to substantiate this conclusion so that short-term high-dose hydroxychloroquine can replace the long-term use of hydroxychloroquine to treat medical disorders.

Conflict of interests

Authors declare no conflict of interest.

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