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Original Research Article

OCULAR COMPLICATIONS OF HYDROXYCHLOROQUINE IN A TERTIARY CARE CENTRE-A CROSS SECTIONAL STUDY

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Abstract

Background: Hydroxychloroquine(HCQ) is an effective drug used in the treatment of various connective tissue disorders. The aim of this study is to evaluate the prevalence of HCQ toxicity in patients on HCQ in northern Kerala and to identify various risk factors associated with the same. **Materials and Methods:** This study included125 patients in the age group 20-70 years on HCQ who met the inclusion criteria selected from outpatient Department of Ophthalmology and Rheumatology clinic. Direct interviews, questionnaires, detailed clinical and ophthalmological examination and relevant lab investigations were done. Demographic data, medical history, height, body weight, diagnostic indication for HCQ use and detailed history of HCQ dosing regimen was collected from patient history, questionnaires and past medical records. **Results:** Out of the 125 patients examined, forty-six patients had any one of the ocular findings such as corneal deposits, posterior subcapsular opacification, fundus changes in the form of RPE changes, field defect as paracentral scotoma or OCT changes that could be considered as possible cases of HCQ toxicity. While corneal deposits were detected in 4% of the study population, fundus changes, PSCO, and paracentral scotoma were seen in 10.4%, 12.8% and 13.6% respectively. OCT changes in the form of IS-OS junction disruption, outer nuclear layer thinning, foveal atrophy were seen in 23.2% patients. **Conclusion:** Increased prevalence of ocular findings suggestive of HCQ toxicity were found in HCQ consumption more than 10 years, daily dose 400mg/day, dose>6.5 mg/kg/day, cumulative dose >1000grams and those patients with renal impairment. However, statistically significant results were obtained only with cumulative dose and years of HCQ use as risk factors probably due to inadequate sample size. No age preference was identified in this study. OCT changes were seen in patients with otherwise normal clinical parameters stressing the importance of the same in early detection of toxicity.

INTRODUCTION

Hydroxychloroquine(HCQ) is an effective drug used widely for the management of a variety of autoimmune disorders- its role well established in the field of rheumatology and dermatology for the treatment of Rheumatoid arthritis and SLE with emerging roles in the field of oncology. But it is well known that hydroxychloroquine may have toxic effects in eye especially retina. Retinal toxicity is the major and most serious irreversible side effect of HCQ.[1] After five to seven years of use or cumulative dose of 1000g, HCQ risk of toxicity increases to 1%.[2] At the same time, there are evidences that suggest that many patients may consume HCQ for many years without problems, while few patients develop retinal photoreceptor dysfunction at very low cumulative doses.[3]

HCQ Retinopathy is characterised by bilateral pigmentary changes in the macula due to atrophy of retinal pigment epithelium with sparing of the foveal area-"Bull's eye maculopathy".[4] But at first changes occur in the ganglion cells and photoreceptors of the retina. Later, retinal pigment epithelium which adversely affects retinal cell metabolism and leads to slow and chronic effects. The exact pathophysiologic mechanism of HCQ retinal toxicity is still uncertain. Whorl like corneal epithelial deposits, the condition called vortex keratopathy (cornea verticillata) may occur in around 10% of patients taking HCQ. The occurrence of corneal deposits was found as a

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statistically significant predictor of mild retinopathy.[5]

Retinal toxicity that may be irreversible can develop in individuals who take HCQ especially when higher risk criteria are present.[6] Retinal degenerations from hydroxychloroquine can continue to progress even after discontinuation of the drug. Hence it is strongly recommended to conduct ophthalmic screening of patients to detect early retinopathy and discontinue therapy if changes are suspected.

It is of prime importance that ophthalmologists are accustomed to recognise the patterns on HVF that indicate toxicity to hydroxychloroquine. The patterns are- Partial or complete ring defect between 2–6 degrees with central sparing on 10-2 white tests; central scotoma affecting one or more of the 4 points around fixation on 24-2 testing (more evident on deviation plots).[7]

Early detection of HCQ toxicity before development of visual symptoms could improve the life of many who are regularly on medication for decades. With increasing incidence of autoimmune disorders and subsequent increase in use of HCQ, it is quite important to probe further in this direction. The aim of this study is to evaluate the frequency of HCQ retinopathy in patients on HCQ in northern Kerala and to identify various risk factors associated with the same.

MATERIALS AND METHODS

It was a Cross sectional study carried out from outpatient unit under Department of Ophthalmology and Rheumatology clinic under department of General Medicine, Government Medical College, Kozhikode over 1 year one year from January 2020 to June 2021. This study included patients on Hydroxychloroquine over one-year duration who attended Ophthalmology or Rheumatology outpatient unit during the study period.

Inclusion Criteria

Patients with age 20-70 years who were on Hydroxychloroquine for a period of more than 1-year duration.

Exclusion Criteria

Patients with optic nerve or retinal pathology, glaucoma, previous intraocular or refractive surgeries

- Patients with refractive error of more than ±6Ds or ±3Dc
- Patients with media opacity inhibiting OCT examination
- Patients who were on other drugs which are known to cause retinal disease
- Patients who were not giving consent for the study

Sample Size

According to a study conducted by Michael MF et al,[8] among patients on HCQ recruited from Collagen Disease clinic at the Los Angeles County hospital published in American Journal of Ophthalmology, prevalence of corneal deposition of HCQ occurred in 28%

According to the formula, n= 4pq/d2

Where,

- P= Prevalence from previous study
- Q= 100-p
- D= allowable error

Sample size is calculated as 127

Methodology

Subjects in the age group 20-70 years on HCQ for more than a year were selected from outpatient department of ophthalmology and rheumatology clinic. Informed consent was taken from patients. A detailed history including details of age of the patient, sex, indication, coexisting diseases, dosage and duration of HCQ use was taken. External ocular examination was carried out using Slit lamp to look for corneal deposits and PSCO. Visual acuity was assessed using illuminated Snellen's chart for distance vision and trial of glasses done to determine best corrected visual acuity. Near vision was assessed using Snellen's near vision chart after appropriate correction. Similarly, colour vision and contrast sensitivity was determined by Ishihara's chart and Pelle Robertson chart respectively. Fundus examination was done by slit lamp microscopy with 90 D and direct ophthalmoscopy after dilatation of pupil with tropicamide (0.5%) eye drops. Spectral domain Optical coherence topography of macula was done using DRI OCT TRITON machine. Macula was analysed to look for morphological changes suggestive of HCQ Retinopathy such as IS OS disruption, perifoveal thinning of outer layers. Foveal thickness was noted. Foveal thickness <172µm or >250µm was taken as abnormal. Presence or absence of thinning of whole macula or part of the macula was noted. HVF Perimetry 10-2 was carried out on both the eyes. Presence of a partial or total ring scotoma between 2-6 degrees with central sparing was taken as a positive evidence of HCQ related changes. Paracentral points were considered defective when their threshold on the total deviation plot had a less than p=0.01 chance of being normal. Lab investigations including RFT and LFT were done by all patients.

Statistical Analysis

Data was entered to Microsoft Excel and assessment was done by using SPSS Software. Descriptive statistics was calculated using mean(±SD) for normally distributed quantitative variables. Qualitative data was expressed as frequency and percentage. In addition to this, Pearson's correlational analysis was used to evaluate correlation of possible HCQ toxicity with risk factors associated. Statistical analysis was considered when $p<0.05$.

Ethical Considerations

Written informed consent was obtained from all patients willing to take part in study in their own language. No interventions were done and there was no alteration in the treatment done for the purpose of study.

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RESULTS

This study included 125 people who were on Hydroxychloroquine for more than 1-year duration. Out of which 93 (74.43%) were females and 32 (25.6%) were males. The main indication of starting HCQ was Rheumatoid Arthritis (78.4%). 71.2% patients had no other underlying disease. The predominant coexisting disease among the patients was Diabetes (9.6%). Best corrected visual acuity was 6/6 in majority of patients. (54%). Eighty-four percent of participants belonged to <60 years and 16% belonged to >60 years. [Table 1]

The mean cumulative dose is 438±380 grams. The cumulative dose in the study group varies between 146 to 2190 grams. [Table 2]

98% of patients had normal colour vision in this study. 2 males had defective colour vision in both eyes which could be congenital. Contrast sensitivity was found to be abnormal in 8 (6.4%) of study population. 4 patients with abnormal contrast sensitivity had changes in OCT macula as well. Around one third patients (33.6%) showed blurring of amsler grid in this study. [Table 4]

In this study, 36.8% patients were detected to have any one of the possible findings suggestive of HCQ toxicity. Majority of the patients had changes in OCT macula analysis which accounted to 23.2%. While paracentral scotomas were detected in 13.6%, RPE changes were noted in 10.4% of study group. Subepithelial deposits were identified in only 4% of the study subjects. [Table 5]

Around 50% of patients in the study group received HCQ in the dose 400mg /day. 32.8% patients were on 200mg/day while 16.8% patients on 300mg/day. Patients who were on 400mg of HCQ per day showed increased prevalence of ocular findings suggestive of possible HCQ toxicity (39.6%) in comparison to other dose groups. (p value .658). Maximum number of patients in our study were in the age group of <60 years, which contributed to about 84%. Features of possible ocular toxicity with HCQ were comparable in both age groups with 35% in age>60 group had any one of the findings as compared to 37% in age<60years group. Majority of patients (92.8%) had received a cumulative dose <1000grams of HCQ. Increased prevalence of HCQ toxicity were found in those patients who had received HCQ in doses more than 1000 grams in total in comparison with those who had received low doses in our study and was statistically significant. [Table 6]

Out of the 18 patients who were on a daily dose of HCQ exceeding 6.5mg/kg, 10(55.5%) showed any of the ocular findings suggestive of possible HCQ toxicity in comparison to 36(33.6%) out of 107 in the group who received daily dose <6.5mg/kg/day. (p value 0.06). [Table 7]

All patients in this study who were on HCQ for a duration more than 10 years showed some findings suggestive of HCQ toxicity. Similarly, increased prevalence was found in 5-10 years group in comparison with those patients who were on HCQ less than 5 years. (p value 0.001). Hence duration of HCQ was determined to be a predictor for HCQ toxicity according to this study. [Table 8]

Table 1: Baseline characteristics of study population

Baseline Characteristics	Study population
Total no of patients	125
Mean age(in years)	48.3±13.2
Sex	Females93(74.4%), males 32(25.6%)
Underlying disease Diabetes Hypertension CAD Old PTB CVA	 12(9.6%) 10(8.0%) 6(4.8%) 6(4.8%) 2(1.6%)
Indication for HCQ use RA SLE Seronegative spondyloarthropathy Scleroderma	 99(79.2%) 17(13.6%) 6(4.8%) 3(2.4%)

Table 2: Cumulative dose of HCQ among study group

Cumulative dose	Frequency	Percentage
<1000 grams	116	92.8%
>1000 grams	9	7.2%

Table 3: Frequency of best corrected visual acuity for distance among study group

Best corrected visual acuity using Snellen's chart for distance vision	Frequency	Percentage
6-Jun	135	54%
9-Jun	75	30%
12-Jun	26	10.40%
18-Jun	9	3.60%

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24-Jun	3	1.20%
Jun-36	0	0
Jun-60	2	0.80%

Table 4: Frequency of colour vision

Colour vision	Frequency	Percentage
Normal	123	98.40%
Abnormal	2	1.60%

Table 5: Prevalence of possible HCQ toxicity

Ocular findings	Frequency	Percentage
Subepithelial deposits	5	4%
PSCO	16	12.80%
RPE changes	13	10.45%
Paracentral scotoma	17	13.60%
OCT changes	28	23.20%

Table 6: Analysis of daily dose as a risk factor in possible HCQ toxicity

Dosage(mg)	Total no. of patients	Corneal deposits	PSC	Fundus changes	Field defects	OCT changes
200	41(32.8%)	2	5	5	7	6
300	21(16.8%)	0	3	4	3	6
400	63(50.4%)	3	8	4	7	16

Table 7: Analysis of dose/kg/day as a risk factor in possible HCQ toxicity

Dosage(mg/kg/day)	Total no. of patients	Corneal deposits	PSC	Fundus changes	Field defects	OCT changes
<6.5mg/kg/day	107	3	12	11	12	21
>6.5 mg/kg/day	18	2	4	2	5	7

Table 8: Analysis of duration of HCQ use as a risk factor in possible HCQ toxicity

Years of HCQ(in years)	Total no. of patients	Corneal deposits	PSC	Fundus changes	Field defects	OCT changes
<5	97	4	9	9	14	15(16.8%)
10-May	23	1	5	2	0	9(34.7%)
>10	5	0	2	2	3	4(80%)

DISCUSSION

Possible cases of ocular manifestations which included corneal deposits, posterior subcapsular opacification, fundus changes and OCT changes were 36.8 % in this study which showed increased percentage since these findings are nonspecific and could be attributed to conditions other than HCQ toxicity.

Michael MF et al demonstrated 28% of 94 eyes using HCQ in the dose 800mg/day with corneal deposits.[8] Study by Easterbrook et al showed <5% incidence of HCQ corneal infiltrates in patients on 400mg/day.[9] Similar results were obtained by Grierson et al which showed 6(0.8%) of 758 patients with corneal deposits.[9] Four patients out of those with corneal deposits were on daily dose>6.5mg/kg/day. In our study, out of the 5 patients with corneal deposits, 2 were on dose>6.5 mg/kg/day and 1 patient had cumulative dose more than 1000 grams.

Incidence of HCQ Retinopathy ranges between 0.48 to 6%, variation mainly due to different definitions of retinopathy and use of different doses. The highest incidence of 4% occurred in a prospective study of 99 patients conducted by Rynes et al, but majority of cases were premaculopathy rather than true maculopathy.[10] In another prospective study by Mavrikakis et al consisting of 526 patients, the overall incidence of irreversible hydroxychloroquine retinopathy was 0.38%.[6] All these studies support the view that HCQ Retinopathy is rare. In this study too, definite cases of HCQ Retinopathy could not be isolated. However, we were able to trace 13(10.45%) patients with premaculopathy.

Patterns of HVF that indicate toxicity include partial or complete ring scotoma between 2-6 degrees with central sparing on 10’2 white test, central scotoma affecting one or more of the 4 points around fixation on 24’2 or more diffuse central/paracentral defect on 10’2 red visual fielding testing.[7] In our study, paracentral scotoma was found to occur in 17(13.6%) patients among which 12 patients had OCT changes as well.

Daily dosage is considered one of the most important risk factor in the development of HCQ Retinopathy.[12] At a dosage of <6.5 mg/kg lean body weight/day, no cases of HCQ Retinopathy was observed by Mackenzie et al which led him to the conclusion, this to be the recommended dosage at which patients would not be at risk. Despite this, 14 cases of hydroxychloroquine retinopathy occurring at this dosage are reported in the review by Yam et al, and up to 21 cases have been reported in other studies.[13] In this study, 11 patients with possible retinopathy were observed in daily dose <6.5mg/kg/wt.

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In the study conducted by Marmor MF et al led to the conclusion that kidney disease markedly increases the risk of retinal toxicity. A drop in kidney function by 50% leads to an approximate doubling of the risk of retinopathy. Although hydroxychloroquine is partially cleared by the hepatic system, no increase in the risk of retinal toxicity from liver disease was identified in this study.[14] Our study also identified increased prevalence of toxicity in patients with renal impairment, but statistically significant results could not be obtained probably due to inadequate sample size.

CONCLUSION

Out of the 125 patients, 46(36.8%) patients had any one of the findings ocular findings suggestive of possible HCQ toxicity. Corneal changes in the form of sub epithelial deposits were identified in 5(4%) of study subjects. Defects in colour vision and contrast sensitivity were present in 2(1.6%) and 8(6.4%) patients respectively. Cases of possible HCQ Retinopathy picked up by fundus changes in the form of RPE mottling accounted to 10.4%.

OCT macula changes identified include IS OS junction disruption (4.8%), perifoveal thinning of outer retinal layers (10.4%), central foveal thinning (8.8%) and whole macular thinning (1.6%). Definite cases of HCQ retinopathy could not be detected in this study emphasizing low frequency of toxicity associated with the drug. Cumulative dose as well as years of HCQ consumption were identified as significant risk factors predisposing to HCQ toxicity by Pearson's Chi square test. Baseline visual assessment with annual reassessment after starting medication should be a practice especially in high risk category.

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