Original Article
DOI: https://doi.org/10.70749/ijbr.v3i4.999

INDUS JOURNAL OF BIOSCIENCE RESEARCH
https://induspublishers.com/IJBR
ISSN: 2960-2793/ 2960-2807

Adverse Effects of Hydroxychloroquine in Different Connective Tissue Disorders Used for Dermatological Purpose

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ARTICLE INFO

Keywords
Autoimmune Disease, Hydroxychloroquine, Cutaneous Manifestation, Gastrointestinal Symptoms.

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Declaration
Authors' Contribution: The authors equally contributed to the study and approved the final manuscript.
Conflict of Interest: No conflict of interest.
Funding: No funding received by the authors.

Article History
Received: 28-01-2025, Revised: 24-03-2025
Accepted: 05-04-2025, Published: 16-04-2025

ABSTRACT

Introduction: Hydroxychloroquine (HCQ) is one of the most frequently used drugs in dermatology with a wide variety of uses. This study was conducted to determine adverse effects of HCQ when given in patients of auto immune disorders. **Objectives:** To determine frequency of adverse effects of hydroxychloroquine in all patients using hydroxychloroquine for different connective tissue disorders used for dermatological purpose. **Study design and setting:** Cross sectional study was conducted at the Department of Dermatology, Civil Hospital Karachi during the period from July 9, 2024 to January 8, 2025. **Methodology:** Patients aged 12 to 70 years of both genders already diagnosed cases of connective tissue disorder taking hydroxychloroquine for more than 3 months visiting derma OPD for follow-up check-up were enrolled using non-probability consecutive sampling technique. Study was conducted after approval of hospital ethical committee and written informed consent of patients. Demographic data was noted. Adverse effects of hydroxychloroquine were noted. Data was entered and analyzed using SPSS 22. **Results:** In our study 167 patients were enrolled with mean age of 37.52±16.6 years, minimum age was 12 years and maximum age was 37.52 years. There were 24% (40) male patients and 76% (127) were female patients. Mean duration of HCQ use was 2.34±0.88 years. Most common adverse effects noted in our study was dermatological manifestations including skin hyperpigmentation in 28.1% (47) patients followed by urticarial rash in 13.8% (23), second most common involved system was gastrointestinal system including nausea in 10.8% (18), diarrhea in 9% (15), headache in 9.6% (16), heart blocks were observed in 8.4% (14) patients least common adverse effects included were myopathy in 7.2% (12) and retinal toxicity in 3.6% (6) patients only. **Conclusion:** Cutaneous and gastrointestinal symptoms are most commonly reported adverse effected by HCQ when used in patients of autoimmune disease.

INTRODUCTION

Hydroxychloroquine (HCQ) has been approved since 1955 for the prevention and treatment of malaria. Since then, its use has been extended to effectively treat a number of autoimmune disorders, such as systemic lupus erythematosus and rheumatoid arthritis. [1] Evidence suggests that HCQ may also have potent antiviral properties. This discovery prompted recent investigations for the potential use of this drug to treat patients with COVID-19, a novel infection caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) initially reported in Wuhan, China, in December 2019, [2] resulting in more than 200,000 deaths worldwide by April 2020. [3]

Hydroxychloroquine has antimalarial, anti-inflammatory, immunomodulatory, anti-infective, antitumoral, metabolic and antithrombotic effects. [4] It is metabolized mainly by CYP3A4 to active metabolite desethylhydroxychloroquine and inactive metabolites desethylchloroquine and bidesethylchloroquine. [5] Various measurement methods have been developed for the quantitation of hydroxychloroquine levels. Liquid chromatography-mass spectrometry (LC–MS/MS) is a major technique in bioanalysis with its high sensitivity, selectivity and accuracy. [6]

It is generally well tolerated by patients; however, it may cause some adverse effects. [5] In one study predominant gastrointestinal adverse effects were found i.e nausea in 12%, diarrhea in 18%, headache in 12%, and urticaria in 12%. [7] Retinal toxicity was found in 7.5% patients. [8] Myopathy was found in 18.4% of the patients. [9] Decreased hearing was reported in 8% patients. [10] Heart block was found in 9.4% patients. [11] Skin hyperpigmentation was found in 29.2% patients. [12]

The rationale of this study is to determine spectrum of adverse effects of hydroxychloroquine in different connective tissue disorders used for dermatological purpose. Different case reports and small studies have

reported various adverse effects but no comprehensive study is available regarding HCQ adverse reaction affecting different body systems. As hydroxychloroquine is very commonly used drug for various autoimmune and connective tissue disorders like Systemic lupus erythematosus and Dermatomyositis it is pertinent to determine full spectrum of adverse effects encompassing all body organs so that patients' can be counselled about anticipated adverse effect and if reported treated earlier.

Objective

To determine frequency of adverse effects of hydroxychloroquine in all patients using hydroxychloroquine for different connective tissue disorders used for dermatological purpose.

MATERIALS AND METHODS

This cross-sectional study was conducted at the department of dermatology, Civil Hospital Karachi from July 9, 2024 till January 8, 2025. Patients aged 12 to 70 years of both genders already diagnosed cases of connective tissue disorder taking hydroxychloroquine for more than 3 months visiting derma OPD for follow-up check-up were included. Patients of connective tissue disorder having chronic illness including CLD, CKD, COPD or having malignancy including leukemia and lymphoma determined on medical record. Patients of connective tissue disorder with celiac disease or chronic diarrhea before start of treatment determined on medical record. Patients of connective tissue disorder with impaired vision or hearing before start of treatment determined on medical record. Sample size was calculated using WHO calculator keeping 95% confidence level, 4% absolute precision, and 7.5% expected frequency of adverse effect. [8] Sample size was 167 patients. Patients were enrolled using non probability consecutive sampling technique.

Outcome assessment

Adverse effects: Following adverse effects was studied:

- **Central nervous system toxicity**
  - **Headache:** Pain in bilateral temporal region of more than VAS 4 for more than 2 weeks was taken as significant adverse effect.
- **Gastrointestinal toxicity**
  - **Nausea:** Unpleasant feeling of regurgitation of food was labelled as nausea
  - **Diarrhea:** Passage of 2 or more lose stool (Bristol grade 3 or more) per day was labelled as diarrhea
- **Dermatological toxicity**
  - **Urticarial rash:** Sudden appearance of maculopapular rash after drug intake was labelled as urticarial rash.
  - **Skin hyperpigmentation:** Dark pigmentation of skin reported by patient was labelled as skin hyperpigmentation.
- **Cardiac toxicity**
  - **Heart blocks:** It was determined on ECG showing 1st degree heart block (prolonged PR interval), 2nd degree heart block (progressively increasing PR interval with missed beat) or 3rd degree heart block (complete dissociation of atrial and ventricular contractions)
- **Ophthalmological toxicity**
  - **Retinal toxicity:** It was determined by presence of bull's eye maculopathy, evident in fundus changes in central visual field
- **Musculoskeletal toxicity**
  - **Myopathy:** It was determined by presence of muscle pain (VAS more than 4) for more than 2 weeks with raised lactate dehydrogenase level, creatine kinase level and aldolase level

Data collection procedure

After approval from hospital ethical board, patients fulfilling the selection criteria was enrolled from dermatology OPD of Civil Hospital Karachi. A written informed consent was taken from patients after explaining the purpose, benefits and risk of study. Demographic data including age, gender and duration of HCQ use was noted. Complete history was taken and physical examination was done. Patients were assessed for hydroxychloroquine adverse effects as per operational definition. Data was entered in specially designed proforma.

Statistical analysis

Data was entered and analyzed by using SPSS version 22.0. Mean and standard deviation was calculated for quantitative variables. Shapiro–Wilk test was used to check normal distribution of data. Frequency and percentages were calculated for categorical variables. Effect modifiers like age, gender and duration of hydroxychloroquine use was addressed through stratification of data. Post stratification chi square was applied. P value ≤ 0.05 was taken as statistically significant (Fisher's test exact in cases $n \leq 5$).

RESULTS

In our study 167 patients were enrolled with mean age of 37.52±16.6 years, minimum age was 12 years and maximum age was 37.52 years. There were 24% (40) male patients and 76% (127) were female patients. Mean duration of HCQ use was 2.34±0.88 years. Regarding co-morbid conditions diabetes was present in 35.9% (60), hypertension in 30.5% (51), smoking in 16.2% (27)

and obesity was present in 37.7% (63) patients. Most common adverse effects noted in our study was dermatological manifestations including skin hyperpigmentation in 28.1% (47) patients followed by urticarial rash in 13.8% (23), second most common involved system was gastrointestinal system including nausea in 10.8% (18), diarrhea in 9% (15), headache in 9.6% (16), heart blocks were observed in 8.4% (14) patients least common adverse effects included were myopathy in 7.2% (12) and retinal toxicity in 3.6% (6) patients only. Regarding age groups diarrhea was more common in younger age group, p-value 0.05. headache was more common in male patients, p-value 0.001. diarrhea was more common in female patients, p-value 0.023. diarrhea was more common in patients using HCQ for short term use, p-value 0.026. Myopathy was also more common in patients using HCQ for short term, p-value 0.015.

Table 1

Demographic Data of Patients

Variables		Frequency	Percent
Gender	Male	40	24.0
	Female	127	76.0
Age groups	12-45 years	105	62.9
	46-70 years	62	37.1
Duration of HCQ use	Equal to or less than 2 years	97	58.1
	More than 2 years	70	41.9
Diabetes		60	35.9
Hypertension		51	30.5
Smoking		27	16.2
Obesity		63	37.7

Table 2

Frequency of Reported Adverse Effects

Variables		Frequency	Percent
Adverse effects of HCQ	Skin hyperpigmentation	47	28.1
	Urticarial rash	23	13.8
	Nausea	18	10.8
	Headache	16	9.6
	Diarrhea	15	9.0
	Heart blocks	14	8.4
	Myopathy	12	7.2
	Retinal toxicity	6	3.6

Figure 1

Gender Distribution

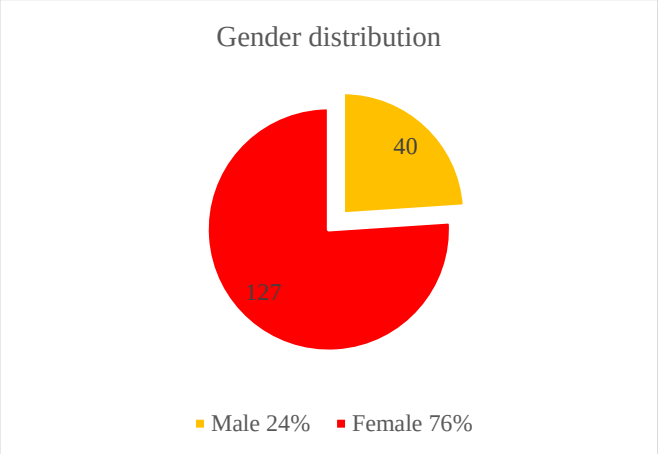

Figure 2

Frequency of Adverse Effects of HCQ

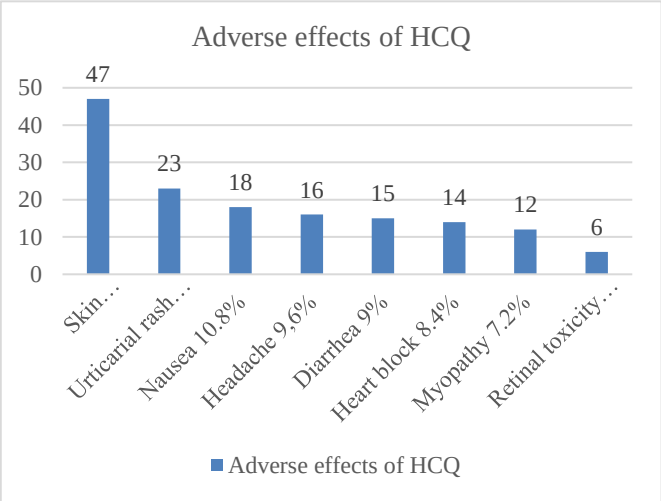

Table 3

Stratification for Frequency of Adverse Effects and Age Groups

Adverse effects			Age groups 12-45 years	Age groups 46-70 years	Total	p-value
Headache	Yes	N	12	4	16	0.416
		%	75.0%	25.0%	100.0%	
	No	N	93	58	151	
		%	61.6%	38.4%	100.0%	
Nausea	Yes	N	8	10	18	0.087
		%	44.4%	55.6%	100.0%	
	No	N	97	52	149	
		%	65.1%	34.9%	100.0%	
Diarrhea	Yes	N	13	2	15	0.052
		%	86.7%	13.3%	100.0%	
	No	N	92	60	152	
		%	60.5%	39.5%	100.0%	
Urticarial Rash	Yes	N	14	9	23	0.830
		%	60.9%	39.1%	100.0%	
	No	N	91	53	144	
		%	63.2%	36.8%	100.0%	
Skin Hyper-pigmentation	Yes	N	27	20	47	0.364
		%	57.4%	42.6%	100.0%	
	No	N	78	42	120	
		%	65.0%	35.0%	100.0%	
Heart Blocks	Yes	N	7	7	14	0.298
		%	50.0%	50.0%	100.0%	
	No	N	98	55	153	
		%	64.1%	35.9%	100.0%	
Retinal Toxicity	Yes	N	4	2	6	0.99
		%	66.7%	33.3%	100.0%	
	No	N	101	60	161	
		%	62.7%	37.3%	100.0%	
Myopathy	Yes	N	5	7	12	0.130
		%	41.7%	58.3%	100.0%	
	No	N	100	55	155	
		%	64.5%	35.5%	100.0%	

Table 4
Stratification for Frequency of Adverse Effects and Gender

Adverse effects			Gender		Total	p-value
			Male	Female		
Headache	Yes	N	10	6	16	0.001
		%	62.5%	37.5%	100.0%	
	No	N	30	121	151	
		%	19.9%	80.1%	100.0%	
Nausea	Yes	N	3	15	18	0.567
		%	16.7%	83.3%	100.0%	
	No	N	37	112	149	
		%	24.8%	75.2%	100.0%	
Diarrhea	Yes	N	0	15	15	0.023
		%	0.0%	100.0%	100.0%	
	No	N	40	112	152	
		%	26.3%	73.7%	100.0%	
Urticarial Rash	Yes	N	5	18	23	0.99
		%	21.7%	78.3%	100.0%	
	No	N	35	109	144	
		%	24.3%	75.7%	100.0%	
Skin Hyperpigmentation	Yes	N	8	39	47	0.189
		%	17.0%	83.0%	100.0%	
	No	N	32	88	120	
		%	26.7%	73.3%	100.0%	
Heart Blocks	Yes	N	2	12	14	0.522
		%	14.3%	85.7%	100.0%	
	No	N	38	115	153	
		%	24.8%	75.2%	100.0%	
Retinal Toxicity	Yes	N	2	4	6	0.630
		%	33.3%	66.7%	100.0%	
	No	N	38	123	161	
		%	23.6%	76.4%	100.0%	
Myopathy	Yes	N	4	8	12	0.484
		%	33.3%	66.7%	100.0%	
	No	N	36	119	155	
		%	23.2%	76.8%	100.0%	

Table 5
Stratification for Frequency of Adverse Effects and Duration of HCQ Use

Adverse effects			Duration		Total	p-value
			Equal to or less than 2 years	More than 2 years		
Headache	Yes	N	8	8	16	0.491
		%	50.0%	50.0%	100.0%	
	No	N	89	62	151	
		%	58.9%	41.1%	100.0%	
Nausea	Yes	N	11	7	18	0.783
		%	61.1%	38.9%	100.0%	
	No	N	86	63	149	
		%	57.7%	42.3%	100.0%	
Diarrhea	Yes	N	13	2	15	0.026
		%	86.7%	13.3%	100.0%	
	No	N	84	68	152	
		%	55.3%	44.7%	100.0%	
Urticarial Rash	Yes	N	12	11	23	0.536
		%	52.2%	47.8%	100.0%	
	No	N	85	59	144	
		%	59.0%	41.0%	100.0%	
Skin Hyper-pigmentation	Yes	N	31	16	47	0.197
		%	66.0%	34.0%	100.0%	
	No	N	66	54	120	
		%	55.0%	45.0%	100.0%	
Heart Blocks	Yes	N	6	8	14	0.228
		%	42.9%	57.1%	100.0%	
	No	N	91	62	153	
		%	59.5%	40.5%	100.0%	
Retinal Toxicity	Yes	N	1	5	6	0.083
		%	16.7%	83.3%	100.0%	
	No	N	96	65	161	
		%	59.6%	40.4%	100.0%	
Myopathy	Yes	N	11	1	12	0.015
		%	91.7%	8.3%	100.0%	
	No	N	86	69	155	
		%	55.5%	44.5%	100.0%	
			97	70	167	

DISCUSSION

Hydroxychloroquine (HCQ) has been approved since 1955 for the prevention and treatment of malaria. Since then, its use has been extended to effectively treat a number of autoimmune disorders, such as systemic lupus erythematosus. [13] HCQ has been used successfully to treat a number of dermatological disorders, and new uses continue to be found even today, most notably, its antiviral effect has been rediscovered, making it a much sought after drug by governments worldwide. [14] Apart from its antimalarial activity, HCQ has antiproliferative, anti-inflammatory, photoprotective, and immunomodulatory effects. HCQ is useful for arthritis, pleuritis, pericarditis, and lethargy. [14] In addition, the drug has a protective effect against irreversible organ damage, thrombosis, and loss of bone mass. It is also known to cause reduction in blood lipids, protection against osteonecrosis, remission of lupus-related nephritis, delayed development of systemic lupus, and protective effects against developing cancer. Additional symptoms such as fatigue, weakness, arthralgia, myalgia, serositis, and mucous membrane ulcers improve in patients with SLE. Also, early HCQ use is associated with delayed onset of SLE. [14]

In our study most common adverse effect were dermatological manifestations including skin hyperpigmentation in 28.1% patients followed by urticarial rash in 13.8%. Same were reported in other studies. Use of HCQ even in COVID-19 treatment also results in dermatological adverse effects. 27.8% experienced exacerbation of psoriatic symptoms, and 22.2% had a relapse of psoriasis after HCQ administration. Whereas many patients developed denovo psoriasis. Dermatologic effects of hydroxychloroquine are poorly understood. It is especially important to monitor for such adverse effects during the potential use of hydroxychloroquine for treatment or prophylaxis. [13] Pelle and Callen have reported that roughly 25% of all dermatomyositis patients experience skin hypersensitivity during HCQ therapy. [15] A cross-sectional study was conducted over a duration of 7 months, during which patients who had received HCQ treatment for >6 months were included. Out of 316 patients, 83 (26.3%) patients presented hyperpigmentation during HCQ treatment.

Hyperpigmentation was presented after a median duration of HCQ treatment of 12 months (interquartile range, 6.0–30.0 months) with a median cumulative dose of 108 g of HCQ (interquartile range, 36–288 g). [16]

In our study second most common adverse effect were GI including nausea in 10.8% patients and diarrhea in 9% patients similarly previous studies reported GI adverse effects 10% after HCQ use and 20% after chloroquine use. [17]

In our study heart block were reported in 8.4% patients. It is also evident from literature that HCQ causes cardiotoxicity. It is recommended that determination of creatine kinase (CK) and lactate dehydrogenase (LDH) in blood is appropriate to screen for cardiomyopathy and should be checked before starting the treatment and then every 3 months. Screen for digoxin use and history of cardiomyopathy or severe heart failure. In such cases electrocardiogram (ECG) during therapy is warranted and watch for depression of ST segment, T-wave inversion and QT interval prolongation. [18] Chatre et al. [19] reported that nearly 85% patients had conduction disorders after a median of 7 years and a high cumulative dose (median 1235 g HCQ). While frequency in our study was low because of low dose and less duration of HCQ therapy.

In our study retinal toxicity was reported in very few patients, 3.6%. Similar frequency was reported by study done in Greece on patients of SLE and rheumatoid arthritis taking HCQ, retinal toxicity was found in 3.4% patients. [20] In another study the prevalence of retinal toxicity assessed by visual acuity, fundoscopy, an Amsler grid, and/or color, vision assessments is estimated between 0.5 and 2%. [21] While in other studies higher frequency was reported. Hydroxychloroquine retinal toxicity is far more common than previously considered; an overall prevalence of 7.5% was identified in patients taking HCQ for greater than 5 years, rising to almost 20% after 20 years of treatment. [22] It was attributed to longer duration of HCQ use in other studies. Retinal toxicity is develops after 5 years of HCQ use while in our study mean duration of use was 2.2 years. The American Academy of Ophthalmology (AAO) recommends that patients on long-term HCQ should visit an ophthalmologist within the first year of treatment for fundus examination. They have found that the risk of toxicity increases toward 1% after 5–7 years of use or a cumulative dose of 1000 g or 460 g of HCQ or CQ, respectively If the baseline fundus examination is abnormal screening tests should be performed annually. [23]

CONCLUSION

Hydroxychloroquine (HCQ) has multiple mechanisms of action, including regulation of immunity, lipid and glucose metabolism, hemostasis, vasoactivity, and tumor control. However, this broad spectrum of action is also at the origin of various side effects, notably including cutaneous, gastrointestinal, ocular and cardiac toxicity. Most of these side effects are reversible, dose dependent and duration dependent if treatment is stopped early, but can have serious consequences if stopped too late.

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