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Original Research Article

A Study to Compare the Prolongation of the Corrected QT Interval of Rheumatoid Arthritis Patients on Hydroxychloroquine

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Abstract

Background: For rheumatoid arthritis (RA) patients, hydroxychloroquine (HCQ) is a staple treatment. Concerns about its cardiovascular safety have been raised after reports of its use and fatal arrhythmias in individuals with coronavirus illness 19.

Aims and objectives: To examine the relationship between HCQ use and corrected QT (QTc) length in RA patients.

Materials and Methods: Hundred subjects (age ≥ 18 years) were studied after dividing them in to Cases (n=50; patients with RA taking HCQ) and Control (n=50; patients without RA not taking HCQ) at the Department of General Medicine of a tertiary care center in Madhya Pradesh. Patient characteristics and laboratory measures, including rheumatoid factor hemoglobin, white blood cells count, platelets, erythrocyte sedimentation rate (ESR), random blood sugar, urea, Creatinine, SGOT, SGPT, serum electrolytes, calcium, and magnesium level, were assessed. QTc length was obtained with the help of 12-lead ECG.

Results: Incidence of QTc prolongation in patients with RA was 11%. Odds for prolonged QTc interval for patients with age >50 years was 3.500 (95% CI = 0.865-14.155), serum calcium <8 was 2.400 (95% CI = 0.540-10.666), and ESR >20 was 0.756 (95% CI = 0.640-0.892). A significant positive correlation was obtained between prolonged QTc with age (r=0.283; p=0.046).

Conclusion: There is a significant increase in risk of QTc prolongation with the use of HCQ in patients with RA.

Keywords: QTc prolongation, rheumatoid arthritis, hydroxychloroquine, fatal arrhythmias

Introduction

For rheumatoid arthritis (RA), hydroxychloroquine (HCQ) is a standard treatment option, either alone or in combination with other disease-modifying anti-rheumatic medications. The acidic cytoplasmic components of the lysosome are neutralized by HCQ, which then alters antigen processing and inhibits toll-like receptors. [1] The accumulation of its metabolite 4-aminoquinolone in the skin,

retina, and muscles is likely responsible for the reported toxicities. [2]

Short-term exposure to HCQ (and the subsequent blocking of potassium channels within myocytes) can cause acute cardiovascular (CV) toxicities, most notably a prolonged QT interval; this can lead to arrhythmic events (i.e., torsades de pointes) when combined with other baseline risk factors like age, sex, high levels of anti-Ro antibodies, and arrhythmogenic congenital long QT syndromes. [3,4] Cardiomyopathy is characterized by concentric hypertrophy, and conduction problems may develop after prolonged exposure to HCQ metabolites. On average, individuals with RA had been taking HCQ for 13 years before developing HCQ-induced cardiomyopathy, and they accounted for 33 of the 42 verified cases. [1,5] Fourteen of the original 42 instances developed third-degree atrioventricular block. However, in long-term HCQ usage, there are no current recommendations for CV screening based on guidelines.

Further concerns for HCQ-associated cardiotoxicity have been highlighted by recent reports of possible connections between concurrent HCQ and azithromycin use and QTc prolongation in people being treated for coronavirus disease 2019 (COVID-19)-associated pneumonia. [6,7]

QTc prolongation was not more common in HCQ users than non-users, and there was no association between HCQ use and QTc length in observational (primarily retrospective) studies of patients with rheumatic disease. However, these studies did not reliably account for the use of other medications known to prolong QTc. [8,9] Therefore, we examined the correlations between HCQ consumption and QTc duration in a RA population free of established CVD, controlling for using other QTc-prolonging drugs.

Materials and Methods

The present prospective observational study was performed on 100 subjects at the Department of General Medicine of a tertiary care center in Madhya Pradesh. Subjects were divided in to Cases (n=50; patients with RA taking HCQ) and Control (n=50; patients without RA not taking HCQ).

Inclusion criteria included age ≥ 18 years old and fulfilment of 2010 ACR RA classification criteria. [10] ECGs were obtained during the first study visit in both groups.

QTc length

The 12-lead ECGs (25 mm/s paper speed and 10 mm/mV amplitude) obtained at the first/baseline study visits were interpreted by a board-certified cardiologist with specialization in electrophysiology blinded to diagnosis. The QT interval was calculated and adjusted for the heart rate using Bazett's formula ($QTc = QT/\sqrt{RR}$). It was evaluated as a continuous and binary variable using≥ 440 and ≥ 500 ms cutoffs. These cutoffs have been associated with an increased risk of clinical cardiac events, including myocardial infarction, cardiac arrest, stroke, and sudden cardiac death.

Patient characteristics and Laboratory measures, including Rheumatoid factor Hemoglobin, WBC count, platelets, ESR, RBS, urea, creatinine, SGOT, SGPT, serum sodium, serum potassium, serum chloride, serum calcium, and magnesium level, were assessed.

Statistical analysis

Data were recorded in the Microsoft Excel program, and statistical analysis was performed by the SPSS program for Windows, version 25 (SPSS, Chicago, Illinois). Continuous variables were presented as mean ± SD, and categorical variables were presented as absolute numbers and percentages. Data were checked for normality before statistical analysis. A descriptive analysis was performed to obtain the general characteristic of the study population.

Categorical variables were analyzed using the chi-square test or Fisher's exact test. Continuous variables were assessed using ANOVA or independent sample t-test.

Pearson correlation (r) was performed to establish the correlation between QTc Prolonged and its risk factors. P<0.05 was considered statistically significant.

Results

Table 1: Characteristics of the patients in both the groups

Characteristics	Cases	Control	P value
Age; years	45.78±13.33	48.82±14.53	0.279
Sex (male/female)	3/47	26/24	<0.001
Hemoglobin	10.53±1.82	10.63±2.14	0.810
WBC count	8858.46±3595.87	7543.40±3110.43	0.053
Platelets	3.37±1.16	2.22±1.12	0.008
ESR	36.92±13.75	26.26±13.44	<0.001
RBS	116.78±36.62	120.80±38.67	0.595
Urea	28.90±15.16	38.20±26.79	0.035
Creatinine	0.66±0.28	1.13±0.77	<0.001
SGOT	34.86±26.06	49.38±43.50	0.046
SGPT	31.20±46.96	39.20±35.84	0.341
Sodium	141.10±6.72	139.54±4.39	0.173
Potassium	4.2428±0.46	4.16±0.46	0.384
Chloride	106.78±4.54	103.40±5.25	0.001
Calcium	8.54±0.58	8.35±0.71	0.139
QT interval	0.36±0.04	0.37±0.40	0.696
QTc	0.45±0.04	0.43±0.03	0.009

Table 2: Characteristics of the Cases with or without QT prolongation

Characteristics	QT prolongation		P value
	No (n=39)	Yes (n=11)	
Age	43.79±13.77	52.82±8.99	0.046
Hemoglobin	10.56±1.85	10.40±1.79	0.803
WBC count	8966.24±3818.01	8476.36±2785.50	0.694
Platelets	3.31±1.23	3.59±0.85	0.485
ESR	36.64±14.21	37.91±12.55	0.790
RBS	115.59±31.24	121.00±53.25	0.670
Urea	27.74±15.80	33.00±12.42	0.315
Creatinine	0.64±0.30	0.729±0.14	0.392
SGOT	35.74±27.97	31.73±18.42	0.656
SGPT	34.03±52.69	21.18±10.67	0.429
Sodium	141.46±7.03	139.82±5.60	0.480
Potassium	4.27±0.45	4.14±0.48	0.430
Chloride	106.694.38	107.09±5.3	0.800
Calcium	8.58460.57	8.40±0.60	0.382

Table 3: Prolonged QTc interval risk assessment in cases

Characteristic	Patient numbers (%)	Prolonged QTc interval		
		Odds ratio	95% CI	P value
Age >50 years	7 (35)	3.500	0.865-14.155	0.070
Calcium <8	1 (50)	2.400	0.540-10.666	0.329
ESR >20	11 (24.4)	0.756	0.640-0.892	0.211

Odds for prolonged QTc interval for patients with age >50 years was 3.500 (95% CI = 0.865-14.155), serum calcium <8 was 2.400 (95% CI = 0.540-10.666), and

ESR >20 was 0.756 (95% CI = 0.640-0.892).

A significant positive correlation was obtained between prolonged QTc with age (r=0.283; p=0.046); however, no significant correlation was obtained for hemoglobin (r=-0.036; p=0.803), WBC count (r=-0.057; p=0.694), Platelets (r=0.101; p=0.485), ESR (r=0.039, p=0.790), RBS (r=0.062; p=0.670), Urea (r=0.145; p=0.315), creatinine (r=0.124, p=0.392), SGOT (r=-0.064; p=0.656), SGPT (r=-0.114; p=0.429), sodium (r=-0.102; p=0.480), potassium (r=-0.114; p=0.430), Chloride (r=0.037; p=0.800) and calcium (r=-0.126; p=0.382).

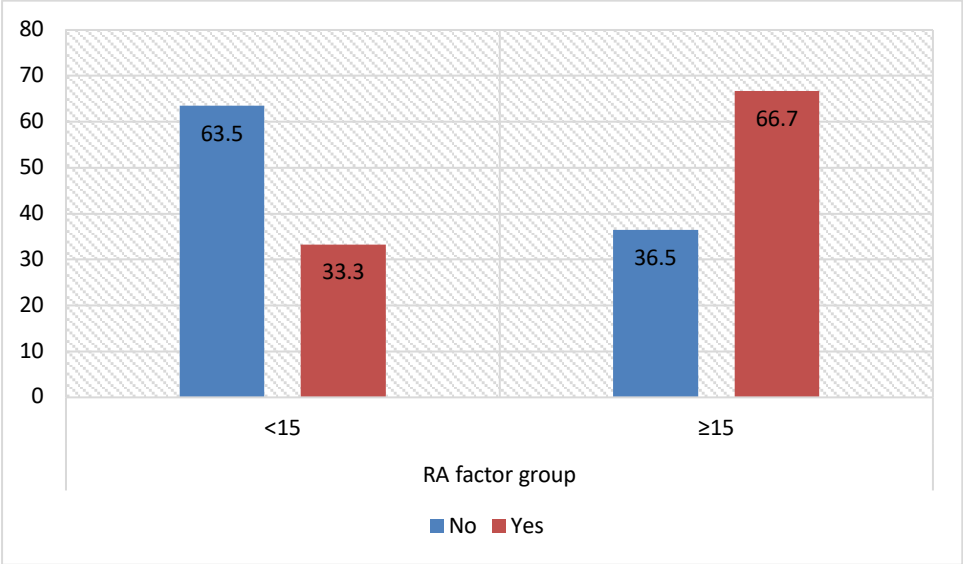

Figure 1: Association between QTc Prolonged and RA factor

Figure 1 showed a significant association between QTc Prolonged and RA factors (p=0.028). Out of 15 patients who reported QTc Prolonged, 10 (66.7%) had RA factors ≥15 as compared to 5 (33.3%) who had RA factors <15.

Table 4: Risk Estimate for QTc Prolonged concerning RA factor

Risk Estimate	Value	95% Confidence Interval	
		Lower	Upper
Odds Ratio for QTc Prolonged (No / Yes)	3.484	1.091	11.122
For cohort RA factor group = <15	1.906	.915	3.969
For cohort RA factor group = ≥15	.547	.347	.862
N of Valid Cases	100		

Discussion

Since prolonged QTc length (defined as > 450 ms in men and > 470 ms in women) independently predicts sudden cardiac death in both the general population and in a few subpopulations (e.g., the elderly, patients with coronary artery disease, and the critically ill), QTc length as an outcome continues to be of utmost interest. [11, 12] Idiopathic QTc prolongation was linked to an almost 30% rise in all-cause mortality in a retrospective cohort study of RA patients (HR 1.28; 95% CI 0.91-1.81, p = 0.16). Additionally, a 50-ms increase in QTc interval was independently linked to a twofold risk of mortality in a prospective cohort of RA patients (HR =2.18, 95% CI 1.09, 4.35), and CRP levels were independently linked to QTc duration. [13]

It was widely reported that COVID-19 patients who took HCQ experienced QTc prolongation and consequent arrhythmia. The change in QTc from baseline to therapy was greater in the HCQ + azithromycin

group compared to the HCQ alone group in an uncontrolled analysis of COVID-19 patients taking HCQ for concomitant pneumonia. Also, one case of torsades de pointes was observed, and up to 19% of people in the previous trial who were given HCQ alone had a QTc > 500 ms (and 21% in the combo group), while 8% had a clinically significant rise > 60 ms.7 However there are very limited study assessing the QTc prolongation in patients with RA.

In present study there was a significant QTc prolongation among cases who were given HCQ as compared to those who have not received HCQ. Also a significant association between QTc Prolonged and RA factors (p=0.028) was obtained in present study. Another important finding of present study was that age is an important risk factor of increasing QTc prolongation (p=0.046). In similar line, Antivalle et al assessed the influence of chronic treatment of HCQ on corrected QTc interval in 52 rheumatic patients and reported that QTc duration was significantly prolonged in patients treated with HCQ (421.26 ± 19.19 vs 410.55 ± 21.18 msec, p < 0.001) compared to those without. [14] There are very limited study confirming the QTc prolongation in RA patients. Apart from a few isolated case reports, the incidence of HCQ-associated QT prolongation at recommended doses appears to be rare. [15]

In light of this, it is essential that doctors and patients who are benefiting from HCQ's use for approved indications feel confident in doing so. [16] Existing patients with rheumatic diseases can continue HCQ if they are infected with coronavirus, as stated by global rheumatology societies such as the British Society for Rheumatology, ACR, and the Asia Pacific League of Associations for Rheumatology. However, other conventional DMARD and biologic therapy must be temporarily discontinued.

Being a cross sectional nature, small sample size and non-randomization, present study findings cannot be applied to large population. There is a need of a large randomized clinical trial to provide more strength to present study findings.

Conclusion

There is a significant increase in risk of QTc prolongation with the use of HCQ in patients with RA. Resultantly it has been proposed that frequent electrocardiographic monitoring be mandatory for patients with RA who receive treatment with HCQ.

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