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Assessment of the Relationship Between Dose and Number of Effective Used Drugs on on QT Interval in Patients with Lupus

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Abstract

Background: Systemic lupus erythematosus is an autoimmune and multi-organ disease. Cardiovascular involvement is one of most important causes of death in these patients. In some studies, it has been observed that the prolongation of the QTc interval is a prognostic factor in cardiovascular failure.
Objectives: In this study, we intended to assess the role of drugs used in treating patients with lupus on the prolonged QTc interval.
Methods: This descriptive-analytical study was carried out on 150 patients with SLE referring to Rheumatology Clinics in the City of Arak during 2014 and 2015. Then, ECGs were taken from all patients in two phases, first on admission and second six hours later. The QTc interval was determined using Bazett's formula. The results were analyzed using SPSS version 16 software.
Results: The mean age of the studied patients was 35.36 $\pm$ 11.8 years and 80.7% were females. An anti-Ro/SSA antibody and treatment with hydroxychloroquine were significantly associated with the prolongation of QTc in patients; however, the duration and dosage of hydroxychloroquine did not affect the QTc interval.
Conclusions: Based on the obtained results, hydroxychloroquine may influence the cardiac condition of patients; thus, it needs more studies in this field.

Keywords: Systemic Lupus Erythematosus (SLE), Hydroxychloroquine, QTc Interval

1. Background

Systemic lupus erythematosus (SLE) is an autoimmune, chronic, progressive disease involving multiple organs that presents with a variety of clinical manifestations and antibody profiles (1). The precise etiology of the disease is not yet known; nevertheless, it has been observed that some factors such as nutrition, female hormones, occupational exposures (such as to silica and mercury), smoking, stress, genetics, and viral infections such as the Epstein virus infection are associated with the progression of the disease (2, 3). Lupus disease often involves women at the childbearing age. The early diagnosis and rapid treatment are important for lupus patients. The prevalence of this disease is between 14.6 and 64 per 100,000 population in the United States. Furthermore, it has been observed that the prevalence of this disease among African Americans is 2 to 4 times that of other people (4). The early clinical manifestations of patients with SLE include weakness, myalgia, fever, anorexia, and weight loss (3).

Given the advancement and development of clinical interventions in the past few decades, there have been significant alterations in the main causes of death in patients with SLE and the involvement patterns of the disease. Today, cardiovascular disease is the main cause of death in SLE patients (5). The considerable point is that patients with lupus are at a higher risk of developing cardiovascular diseases than the general population. Coronary artery disease, myocarditis, endocarditis, valvular disease, and pericarditis are the fundamental manifestations of cardiac involvement in SLE patients (6).

Electrocardiography (ECG) is an inexpensive, available, non-invasive tool potentially capable of the diagnosis of cardiovascular disorders associated with lupus disease, including rhythm disorders and repolarization abnormalities. Abnormal repolarization is usually revealed by a prolonged modified QT interval. These ECG abnormalities are

associated with an increased risk of cardiac arrhythmias and sudden cardiac death (7, 8). The early diagnosis of these abnormalities and electrocardiographic abnormalities may be of prognostic value, playing an important role in determining the prognosis of the disease (8).

2. Objectives

Given the importance of QT interval and its significant role in the incidence of cardiac disorders and since heart anomalies are among the most important causes of death in lupus patients, in the current study, we decided to examine the role of drugs used in treating lupus patients in the prolonged QTc interval. Thus, we can take an effective step to reduce the cardiac complications of such patients if there is a significant association between drugs and the incidence of this disorder in these patients.

3. Methods

This descriptive-analytical study was carried out on 150 outpatients and hospitalized patients with SLE referring to the Rheumatology Clinic of Amiralmomenin Hospital and Imam Reza Polyclinic in the City of Arak during 2014 and 2015. In this study, patients with SLE were diagnosed based on the diagnostic criteria of the American College of Rheumatology (9) that were involved in the disease for at least one year in both genders and age groups ranging from 18 to 50-years-old. The patients were enrolled according to the inclusion criteria of the study.

After including patients in the study, a checklist containing demographic and clinical data was completed for each patient. The checklist contained information like age, gender, duration of involvement in the disease, family history of lupus, family history of other autoimmune diseases, type and duration of any drug used to treat lupus, and any other disorder (other than lupus; including NSAID, prednisolone, antimalarial (chloroquine and hydroxychloroquine), azathioprine, methotrexate, mycophenolate mofetil, antidepressant, cyclophosphamide, ARB, CCB, ACEI, HCQ, and IVIG), the history of other autoimmune diseases in the individual, and the patient's medical and medicinal history (other than the drug used to treat lupus).

Next, ECGs were taken from all patients in two phases, first on admission and second six hours later. A standard ECG was taken with a paper output of 25 mm/s and 12 leads when resting at a heart rate of 60 and 100 bpm. Then, the QT interval, defined from the beginning of the QRS wave to the end of the T wave, was blinded by an expert cardiologist and measured relative to the patient information. This measurement was performed in three successive cycles in lead II. In the event of a conflict with the size measured by the device, the measurement was performed again to reduce the error. The second ECG was taken in the same condition in the next referral and QTc was calculated by using the values obtained from the two electrocardiograms and Bazett's formula (QT interval divided by square RR).

3.1. Inclusion Criteria of the Study

We included patients with the following conditions: (1) a lupus diagnosis in the age range of 18 to 50 years of both genders; (2) informed consent; (3) lack of the history of ischemic heart disease (IHD), congestive heart failure (CHF), moderate to severe valvular disease, atrial fibrillation, bundle branch block (BBB), or electrolyte disorders (such as potassium, magnesium, and calcium reduction); (4) normal ECG when resting; (5) high-quality ECG records for QT interval; and (6) not being involved in intracranial hemorrhage (ICH).

3.2. Exclusion Criteria

The exclusion criteria included (1) dissatisfaction with continuing participation in the study; (2) ischemic heart disease (IHD); (3) bundle branch block (BBB); and (4) early electrophysiological heart disorders affecting the QT interval.

After collecting the data, they were analytically, descriptively, and statistically analyzed by SPSS version 16 software. The central (mean) and dispersion (standard deviation) indices were used for descriptive statistics. The chi-square test was used to analyze the relationship between qualitative variables. Pearson correlation was used to investigate the relationship between quantitative variables.

3.3. Ethical Approval

All ethical principles were observed as per the ethics protocol enacted by the Research Ethics Committee of Arak University of Medical Sciences (ethics code: 93-171-10).

4. Results

The mean age of the studied patients in this review was 35.36 years with a standard deviation of 11.8 years. Moreover, 80.7% of the patients were females and 19.3% were males. The frequency of anti-lupus drugs used in the studied patients was as follows: prednisolone (99.3%), hydroxychloroquine (66%), pulsed methylprednisolone (32%), azathioprine (24.7%), cyclophosphamide (pulse therapy) (23.3%), mycophenolate (14%), methotrexate (6.7%),

cyclosporine (5.3%), rituximab (2.7%), IVIG (2.7%), and cyclophosphamide (0.7%).

The mean size of the QTc interval in two ECGs taken was 413.1 milliseconds with a standard deviation of 46.67 milliseconds. In addition, examining the mean QTc interval of patients revealed that 47 out of 150 patients (31%) had a QTc interval of more than 440 milliseconds. Concerning the correlation between quantitative variables using the nonparametric Spearman test, it was specified that the mean QTc had no significant relationship with the disease duration and the age of the patients (P = 0.118) (Table 1).

Table 1. Investigating the Relationship Between QTc Rate and Age and Duration of Disease

Variable	Spearman Correlation	P Value
Age	0.128	0.118
Disease duration	0.094	0.251

Comparing the characteristics of patients with prolonged QTc and normal QTc, it was observed that the presence of anti-Ro/SSA antibodies was significantly related to the prolonged QTc in patients (P = 0.5) (Table 2). Furthermore, in the comparison of patients with prolonged QTc and normal QTc, we observed a significant difference in consuming hydroxychloroquine and ARB between these groups (P = 0.003); the details are presented in Table 3.

Table 2. Comparison of Characteristics of Patients in the Two Groups[a]

Variable	Normal QTc (N = 103)	Prolonged QTc (N = 47)	P Value
Age	34.11 ± 83.55	36.12 ± 53.47	0.5
Disease duration	4.4 ± 41.87	4.5 ± 89.2	0.4
Involvement in chronic disease	56 (54)	24 (53)	0.56
Gender (female)	82 (80)	39 (83)	0.6
Family history of lupus	5 (4)	4 (58)	0.4
Family history of autoimmune disease	3 (3)	0	0.2
Involvement in autoimmune disease	25 (24.3)	11 (23.4)	0.7
Antibodies against SSA	28 (27)	27 (57)	0.0001

[a]Values are expressed as No. (%) or mean ± SD.

Table 4 shows the results of the Mann-Whitney test on the relationship between the duration of consumption and the dose of hydroxychloroquine. As can be seen, there was no significant relationship between the dose and duration of hydroxychloroquine consumption and QTc (P = 0.807).

Table 3. Comparison of Drug Consumption of Patients in the Two Groups[a]

Variable	Normal QTc (N = 103)	Prolonged QTc (N = 47)	P Value
Hydroxychloroquine	60 (58.3)	39 (83)	0.003
Salicylate	25 (24.3)	10 (21.3)	0.6
Prednisolone	102 (99)	47 (100)	0.5
Mycophenolate	13 (12.6)	8 (17)	0.4
Methotrexate	6 (5.8)	4 (8.5)	0.5
Pulsed cyclophosphamide	26 (25.2)	9 (19)	0.41
Pulsed methylprednisolone	32 (31)	16 (34)	0.16
Cyclosporine	5 (4.9)	3 (6.4)	0.69
Azathioprine	24 (23.3)	13 (27.7)	0.5
Rituximab	4 (3.9)	0	0.17
IVIG	4 (3.9)	0	0.17
ACE-I	4 (3.9)	6 (6.4)	0.5
ARB	51 (50)	14 (30)	0.024
CCB	33 (32)	14 (30)	0.7
Beta blocker	20 (19.4)	10 (21.3)	0.7
Alpha blocker	8 (7.8)	2 (4.3)	0.4
Diuretics	23 (22.3)	14 (28.3)	0.4
SSRI	11 (10.7)	3 (6.4)	0.4
TCAs	3 (2.9)	3 (6.4)	0.3
BZD	9 (8.7)	5 (10.6)	0.7
Antipsychotics	1 (1)	1 (2)	0.5
Antiepileptic	17 (16.5)	7 (15)	0.8

[a]Values are expressed as No. (%).

Table 4. Comparison of Dosage and Consumption Duration of Hydroxychloroquine in Patients in the Two Groups

Variable	Normal QTc (N = 103)	Prolonged QTc (N = 47)	P Value
Mean consumed dosage	283.33	333.33	0.807
Mean consumption duration	4.11	4.87	0.627

5. Discussion

As previously explained, patients with SLE are at a high risk of mortality and morbidity due to atherosclerotic cardiovascular diseases. The interval between the modified

QT is introduced to be a determining and predictive parameter in the incidence of cardiovascular disease (10). The present study was carried out to determine the role of drugs used in the treatment of lupus patients in the QT interval. In this descriptive-analytical study, we assessed 150 outpatients and hospitalized patients with SLE referring to the Rheumatology Clinic of Amiralmomenin Hospital and Imam Reza Polyclinic in the City of Arak during 2014 and 2015 for disease duration, antibodies against SSA, type, dose, and duration of the consumption of drugs, and QTc.

We observed that the mean age of the studied patients was 35.36 $\pm$ 11.8 years and 80.7% of them were females. In a study performed by Tessier et al. in 2011, the mean age of patients was 44.8 $\pm$ 14.8 and 91% of them were females (11). In another study conducted again by him and his colleagues in 2015, the mean age of the patients was 35.2 $\pm$ 13.8 years and 88% of the patients were females (8). Therefore, the results of these studies are consistent with each other, which is due to the increased incidence of lupus among women at the peak of their childbearing age.

A recent study revealed no significant relationship between the patients' age, the duration of the disease, and the patients' gender at a significance level of 0.05. This is while the results of this study indicated a significant increase in the frequency of prolonged QTc in patients with positive anti-Ro/SSA antibodies. The same result was also seen in the study performed by Bourre-Tessier et al. (11) that showed 72.2% of patients with prolonged QTc and 38.8% of patients with normal QTc had positive anti-Ro/SSA antibodies. Moreover, in another study by Lazzerini et al. (12), a statistically significant relationship was observed between prolonged QTc and the presence of anti-Ro/SSA antibodies. Thus, the results of these two studies are consistent with those of the current study. This can indicate the fact that anti-Ro/SSA antibodies are associated with prolonged QTc and consequently, a higher risk of cardiovascular disease.

Moreover, the current study found that the consumption of hydroxychloroquine was associated with prolonged QTc; nevertheless, the dose and duration of drug consumption had no significant relationship with prolonged QTc. It was also seen that ARB drug users had significantly lower QTc. However, in a study by Nomura et al. (13), no significant relationship was found between the consumption of hydroxychloroquine and the prolongation of QTc, which is consistent with the results of the present study. On the other hand, some other studies showed that structural changes, especially in the interventricular septum caused by chloroquine, could develop electrical and QT changes in lupus patients (14).

Due to the higher risk of cardiac dysrhythmia in the prolonged QT intervals, as well as the increased risk of mortality in these patients, QTc can be used as a marker for predicting cardiac diseases (15). Hence, it is very important to consider the modifiable and effective factors in QT, such as drugs, to prevent heart disease.

This study faced some limitations including the small sample size of patients and their short-term follow-ups. It is suggested that more studies be conducted in this field in future research by addressing these constraints.

5.1. Conclusions

As an important point, our study indicated that patients with anti-Ro/SSA antibodies in their blood should be more monitored to diagnose their cardiac involvements as soon as possible to reduce the complications. Some other studies can be done based on our results for more evaluation in this field.

Footnotes

Authors' Contribution: All authors were equally contributed to the manuscript preparation and submission.

Conflict of Interests: The authors have no conflict of interest to declare.

Ethical Approval: All the ethical principles were observed as per the ethics protocol enacted by the Research Ethics Committee of Arak University of Medical Sciences (ethics code: 93-171-10).

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