Research Article / Araştırma Makalesi

Metoprolol's Potential Beneficial Effects On Covid-19 Patients

Metoprolol'ün Covid-19 Hastalarındaki Potansiyel Yararları

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Abstract

Background: We aimed to find the potential beneficial effects of metoprolol, which was added to the treatment of COVID-19 patients with drug-induced long corrected QT (di-LQTc) interval.
Materials and Methods: This study was a retrospective study. Hospitalized patient files were scanned, and the data of 160 Covid-19 positive patients who were confirmed by real-time polymerase chain reaction (RT-PCR) between April 1 and June 1, 2020, were analyzed. A total of 52 patients' data with CoVID-19 patients with di-LQTc were scanned and collected in the metoprolol group, and a total of 108 patients' data with CoVID-19 with normal QTc levels were collected in the non-metoprolol group.
Results: The mean age was 48.58±16.52 (48.75% male). The in-hospital mortality rate was 3.125% (n=5). We did not see any malignant arrhythmias in the groups during follow-up. In the metoprolol group, the peak Qtc was 466.50 (458.75-477.50) msec in patients before metoprolol treatment, whereas it decreased to 443 (428.75-453) msec at discharge. Forward conditional logistic regression analysis demonstrated that basal C-reactive protein (CRP) (OR=1.031, 95%CI: 1.001-1.062, p=0.043) was the independent predictor of di-LQTc in Covid-19 patients.
Conclusions: COVID-19 patients with di-LQTc could be treated and we thought we could reverse the QT prolongation by adding metoprolol to the treatment protocol.

Key Words: COVID-19, Drug-induced prolonged QTc, Hydroxychloroquine, Metoprolol tartrate

ÖZ.

Amaç: Bu çalışmada, ilaca bağlı uzun QT (di-LQTc) aralığı saptanmış olan COVID-19 hastalarında aldıkları tedavilere eklenen metoprololün potansiyel yararlı etkilerini bulmayı amaçladık.
Materyal ve Metod: Bu çalışma geriye dönük yapılmış bir çalışmadır. Bu çalışmadaki veriler, 1 Nisan ile 1 Haziran 2020 tarihleri arasında serviste yatırılmış, gerçek zamanlı polimeraz zincir reaksiyonu (RT-PCR) ile hastalığı doğrulanan 160 adet Covid-19 pozitif hastanın dosyaları taranarak elde edildi. Di-LQTc'li toplam 52 hastanın dosyaları taranıp metoprolol grubuna dahil edildi ve normal QTc düzeyleri olan toplam 108 hasta da metoprolol tedavisi almayan grup olarak belirlendi.
Bulgular: Ortalama yaş 48.58±16.52 (% 48.75 erkek) olarak saptandı. Hastane içi ölüm oranı %3.125 (n = 5) olarak bulundu. Takip sırasında çalışmaya alınan hastalarda herhangi ölümcül aritmi görülmedi. Metoprolol grubunda, metoprolol tedavisi öncesi hastalarda pik Qtc 466.50 (458.75-477.50) msn iken, taburculukta 443 (428.75-453) msn'ye düştü. İleri koşullu lojistik regresyon analizi ile, Covid-19 hastalarında bazal C-reaktif protein'in (CRP) (OR = 1.031,% 95 CI: 1.001-1.062, p = 0.043) di-LQTc'nin bağımsız prediktörü olduğunu saptadık.
Sonuç: Di-LQTc'li COVID-19 hastalarının tedavi protokolüne metoprolol eklenerek uzun Qt durumunun geriye döndürülebilir olduğunu düşünmekteyiz.

Anahtar kelimeler: COVID-19, Hidroksiklorokin, Ilaca bağlı uzamış QTc, Metoprolol tartarat

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Introduction

In December of 2019, a pneumonia cluster was discovered for the first time, in China, Wuhan, Hubei (1). The pathogen has been identified as a coronavirus which is liable for the disease and it's now known as Severe Acute Coronavirus Syndrome-2 (SARS-CoV-2) (2). The disease caused by SARS-CoV-2 is known as COVID-19, and it has since spread around the world. COVID-19 lethality cannot be accurately measured since figures are rising all over the world. When compared to seasonal influenza, lethality appears to be higher in older patients (3). The gold standard for COVID-19 diagnosis was previously claimed to be the real-time polymerase chain reaction (RT-PCR) (4). There is currently no reliable, accepted treatment for COVID-19, just palliative treatment of the symptoms, and supportive care. Some studies reported the antiviral properties of hydroxychloroquine against COVID-19 (5-7). Following the encouraging findings of these clinical trials, physicians all over the world were taking notice of using hydroxychloroquine for some of the selected COVID-19 patients. On the other hand, hydroxychloroquine is well known for its serious complications and side effects. In comparison to non-users, patients who have been treated with hydroxychloroquine have a higher chance of developing a drug-induced long corrected QT interval (di-LQTc). That is especially true when hydroxychloroquine is used in high doses or when used in conjunction with macrolide antibiotics. Until the whole world is vaccinated, existing drugs may be used worldwide to help COVID-19 patients, besides their side effects. Nevertheless, some drugs can avoid changes in the electrocardiography (ECG) that could happen in patients using hydroxychloroquine. Metoprolol tartrate ((±)-1-(Isopropylamino)-3-[p-(2-methoxyethyl)phenoxy]-2-propanol L-(+)-tartrate (2:1) salt) is a member of the selective b1-blocker drug and class II antiarrhythmic agent (8). Metoprolol is used in the treatment of acquired long QT syndrome (9). The protective effect of metoprolol is associated with its selective b1-receptor and adrenergic blockade, and it lowers the risk of arrhythmias in the heart and may treat di-LQTc (9). This study aimed to investigate the conceivable beneficial effects of metoprolol on di-LQTc in CoVID-19 patients.

Materials and Methods

For this retrospective conducted a single-center study, we scanned 206 Covid-19 patients data, who were diagnosed with confirmed RT-PCR Covid-19 from a nasal and throat swab and hospitalized within 48 hours of the onset of symptoms because of severe fever (>38°C) or hypoxia (SaO2≤92%) between April 1st and June 1st, 2020, in a private hospital.

Electrocardiogram:

12-lead electrocardiograms (ECG) were obtained at the time of admission to the outpatient clinic or emergency department and HR was noted in all study patients. All ECGs were obtained with the same device (General Electric MAC 2000, GE Healthcare Technologies, Milwaukee, WI, USA). Long QTc is defined as basal QTc>460 msec for women and basal QTc>440 msec for men (10). Every day after taking HCQ treatment, we obtained 12-lead ECG, till the patient was discharged or died. We recorded the ventricular rate, QRS duration, QT interval which was starting from the beginning of the Q wave to the end of the T wave, then the corrected QT interval (QTc) was calculated via the Bazett formula (QTc=QT-interval/ √RR-interval) (10). We calculated consecutive 3 QTc intervals on every day's ECG records from DII lead and averaged QTc was noted. The findings were assessed by a blinded second investigator for quality control.

Data collection

Hospitalized patient files were retrospectively scanned, and the data of 160 Covid-19 positive patients were analyzed. A total of 52 patients' data with CoVID-19 patients with di-LQTc were scanned and collected in the metoprolol group, and a total of 108 patients' data with CoVID-19 with normal QTc levels were collected in the non-metoprolol group. Patients data with coronary artery bypass graft (CABG), basal ECG other than sinus rhythm, electrolyte abnormalities, basal QTc>460 msec for women and basal QTc>440 msec for men, heart rate <55 bpm, blood pressure (BP) <90/60mmHg, already taking QT-prolonging medications, permanent pacemaker, type II or III Av block, Covid-19 patients with QTc prolongation on the 3rd day or later, pulmonary edema, sign of acute left ventricular dysfunction, acute or chronic neoplastic disease, chronic infective disease, moderate-severe chronic kidney disease, type I Brugada syndrome or arrhythmogenic right ventricular dysplasia, chronic liver disease, and already on beta-blocker therapy were not collected to this study (n=46). On the second day of hospitalization, metoprolol tartrate 50 mg tablet once a day was started in patients whose surface ECG was consistent with QT prolongation. Patient data with Covid-19, who had di-LQTc on the 2nd day (n=52) were collected in the metoprolol group, and a total of 108 patients data with CoVID-19 with normal QTc levels during hospitalization were collected in the non-metoprolol group. In the metoprolol group, we added 50 mg metoprolol tablet to each patient and continued hydroxychloroquine and/or macrolide treatments. The patients have well tolerated the drug and we did not change the dosage during the hospital stay or discharge. After discharge, we continued 50 mg metoprolol once a day for 30 days. We did not see any beta-blocker intolerance or bradycardia. When the hospitalized Covid-19 patient had QTc prolongation on the 3rd day or later, we also gave them once a day 50 mg metoprolol for one month, but we did not collect them in this study.

The condition records of patients who develop di-LQTc and malignant arrhythmias were obtained from hospital records and death certificates. The study was approved by the

Istanbul Yeni Yuzyil University Science, Social and Non-Interventional Health Sciences Research Ethics Committee (Number:2020/06-447), and The Republic of Turkey Ministry of Health scientific research platform (Number:2020-05-14T14_03_43). Furthermore, written informed consent to participate in the study was obtained from participants, and the study was conducted under the provisions of the Declaration of Helsinki.

Venous blood samples from the antecubital vein were taken immediately after admission to the hospital. The Chronic Kidney Disease Epidemiology Collaboration equation was used to compute each patient's estimated glomerular filtration rate (eGFR). The formula (kg/m²) was used for calculating body mass index (BMI). A standard auto-analyzer was used to determine the routine blood chemistry results. A Sysmex K-1000 auto-analyzer (Block Scientific, Bohemia, NY, USA) was used to measure blood counts. Samples were centrifuged at 3000 rpm for 10 min, and the supernatant and serum were separated from the samples. Latex-enhanced nephelometry was used to measure c-reactive protein (CRP) levels with high sensitivity. Following detailed examinations, the medical history of each patient was collected by the same investigators. Risk factors were identified for risk factors including diabetes mellitus (DM), age, hyperlipidemia (HPL), hypertension (HT), gender, and smoking status. Patients with prior antihypertensive medication or BP measured at least twice about 140/90 mmHg, were deemed to be hypertensive (11). Patients previously treated with oral antidiabetic and/or insulin or whose fasting blood glucose was measured at least twice ≥125 mg/dL were considered diabetic (12). HPL was considered if total cholesterol >200 mg/dL or low-density lipoprotein cholesterol (LDL-C) >100 mg/dL was measured, or when the patient took a lipid-lowering drug as prescribed by the guideline (13). We considered patients as a smoker if the patients continued to use tobacco products on admission to the emergency service and those who had ex-smokers in the past month. During the follow-up, we gave the treatment according to the recommendations in the COVID-19 Diagnosis and Treatment Guide published by the scientific advisory board of The Republic of Turkey Ministry of Health scientific research platform (14). As treatment regimen, we gave hydroxychloroquine sulfate (200mg/tablet, for the first day 400 mg/tablet b.i.d., and during ongoing for 5-days 200mg/tablet b.i.d.), corticosteroid (methylprednisolone, 40mg intravenous o.i.d. for 5-days), macrolide (azithromycin for the first day 500mg/tablet, and during ongoing for 4-days 250mg/tablet, o.i.d.), favipiravir (200mg/tablet, for the first day 1600mg/tablet b.i.d., then 600mg/tablet, b.i.d. for 4-days), in the metoprolol group (n=52) we gave metoprolol tartrate (50mg/tablet o.i.d. for 5-days) which were described in Table 1. For the discharge of the patients, the condition was sought that their oxygen saturation should be above 95% in room air and fever should not exceed 37.5 degrees in the last 24 hours.

Statistical analysis:

The statistics software package SPSS version 22.0 (SPSS Inc., Chicago, IL, USA) was used to analyze the data. The normal distribution of a continuous variable was assessed using the Kolmogorov-Smirnov test. The T-test or the Mann-Whitney U test was used to compare continuous variables. Normally distributed continuous variables were expressed as mean and standard deviation. If continuous variables did not satisfy the normal assumption, they were expressed as medians and 25th and 75th percentiles. Categorical variables were expressed as numbers (percentage). Categorical variables were compared with the chi-square test or Fisher's exact test. The correlation between variables was performed using Spearman's rank-order correlation analysis. A single-variable logistic regression analysis was carried out, and the variables with a p-value below 0.1, analyzed with multivariate logistic regression analysis. The odds ratio and 95% confidence interval were calculated. Receiver operating characteristic (ROC) curve analysis was performed to determine the basal-CRP's predictive value for di-LQTc. A p-value of <0.05 was considered significant.

Results

This study was conducted with data from 160 Covid-19 patients (48.75% male (n=78); mean age: 48.58±16.52 years) who were confirmed by RT-PCR. The percentage of the in-hospital mortality rate was 3.125% (n=5) of the study population. The rate of mortality had no statistically significant difference among groups (1 (1.92%) vs. 4 (3.70%), p=0.474). Demographic and laboratory findings are described in Table 1. Regarding cardiovascular risk factors, hypertensive patients were significantly higher in the metoprolol group than in the non-metoprolol group (28 (53.84%) vs. 32 (29.62%), p=0.036). In the metoprolol group, the peak Qtc was 466.50 (458.75-477.50) msec in patients before metoprolol treatment, whereas it decreased to 443 (428.75-453) msec at discharge (Table 1). There was no significant difference among the groups in terms of other demographic and clinical findings. When we compare the basal-CRP level, among groups, the basal-CRP level was significantly higher in the metoprolol group than in the non-metoprolol group (85.35 (27.05-163.50) vs. 34.60 (16.60-120.50), p=0.020). Moreover, age, BMI, length of hospital stay, WBC, AST, glucose, urea, and eGFR parameters were significantly associated with basal-CRP (p<0.05) (Table 2). Forward conditional logistic regression analysis demonstrated that basal-CRP (OR=1.031, 95%CI: 1.00.1-1.062, p=0.043) was the independent predictor of di-LQTc in Covid-19 patients (Table 3).

Table 1: Baseline demographic and laboratory characteristics of the patients.

Variable, n (%)	Metoprolol Group, n=52 (32.5)	Non-Metoprolol Group, n=108 (67.5)	p-value
Age, y	52.73±16.66	46.59±16.23	0.161
Male gender, n (%)	20 (38.46)	58 (53.70)	0.201
BMI (kg/m²)	29.42 (26.58-31.54)	27.70 (25.18-31.31)	0.322
HT, n (%)	28 (53.84)	32 (29.62)	0.036
DM, n (%)	12 (23.07)	24 (22.22)	0.932
HL, n (%)	4 (7.69)	14 (12.96)	0.485
Smoker, n (%)	2 (3.84)	22 (20.37)	0.059
COPD, n (%)	2 (3.84)	10 (9.25)	0.389
Mortality, n (%)	1 (1.92)	4 (3.70)	0.474*
Length of hospital stay, days	9.15±3.83	9.67±4.26	0.305
Medications			
Ace inh, n (%)	8 (15.38)	10 (9.25)	0.417
ARB, n (%)	8 (15.38)	14 (12.96)	0.768
Hydroxychloroquine, n (%)	52 (100)	108 (100)	1
CCB, n (%)	18 (34.61)	18 (16.66)	0.072
Statin, n (%)	2 (3.84)	12 (11.11)	0.281
LMWH, n (%)	52 (100)	108 (100)	1
OAD, n (%)	12 (23.07)	24 (22.22)	0.932
Favipiravir, n (%)	52 (100)	108 (100)	1
Macrolide, n (%)	44 (84.61)	76 (70.37)	0.168
Tocilizumab, n (%)	4 (7.69)	10 (9.25)	0.816
Methylprednisolone, n (%)	20 (38.46)	34 (31.48)	0.536
Convalescent plasma, n (%)	2 (3.84)	2 (1.85)	0.593
Laboratory characteristics			
Glucose, mg/dl	103.50 (93.75-120.25)	100.50 (94-113)	1
eGFR (mL/min per 1.73 m2)	100.30 (86.02-111.35)	102.80 (90.32-111.02)	0.456
Neutrophil10^3/uL	3.95 (2.30-4.80)	3.78 (2.76-4.94)	0.586
Lymphocyte 10^3/uL	1.30 (0.75-1.80)	1.20 (0.90-1.60)	0.861
WBC 10^3/uL	5.98 (4.56-7.85)	5.85 (4.82-7.14)	0.821
HTC %	37.20 (32.90-39.82)	39.75 (35.97-42.07)	0.017
Basal-CRP, mg/L	85.35 (27.05-163.50)	34.60 (16.60-72.50)	0.020
Systolic BP, mmHg	126.85±15.26	124.46±10.64	0.166
Diastolic BP, mmHg	77.58±6.78	75.74±6.62	0.201
Sodium, mmol/L	135 (133-138.50)	136.50 (135-140)	0.076
Potassium, mmol/L	4.00 (3.80-4.26)	4.01 (3.83-4.30)	0.731
TSH, uIU/mL	1.25 (0.90-1.65)	1.38 (1.10-1.85)	0.290
Total Calcium, mg/dL	9.15 (8.80-9.66)	9.31 (9.10-9.70)	0.171
Heart Rate (bpm)	78.54±11.75	79.78±11.07	0.647
Basal QTc, msec	434.50 (425.75-442)	425 (415.75-434)	0.005
Peak QTc, msec	466.50 (458.75-477.50)	425 (410-440)	<0.001
Discharge QTc, msec	443 (428.75-453)	420 (404.25-425)	<0.001

*The p-value for categorical data from Chi-square or *Fisher's Exact Test. The p-value for independent samples t-test or the Mann-Whitney U test was used to compare continuous variables. Values are mean±SD or numbers and percentages. Abbreviations: ACE inh, angiotensin-converting enzyme inhibitors; ALT, Alanine Aminotransferase; ARB, angiotensin receptor blockers; AST, Aspartate Aminotransferase; BMI, Body Mass Index; Bpm, beat per minute; CCB, calcium channel blockers; COPD, chronic obstructive pulmonary disease; CRP, C-reactive protein; mmHg, millimeter of mercury; DM, diabetes mellitus type 2; eGFR, estimated glomerular filtration rate; HB, hemoglobin; HL, hyperlipidemia; HT, hypertension; HTC, hematocrit; LMWH, low molecular weight heparin; MPV, Mean Platelet Volume; OAD, oral antihyperglycemic drugs; QTc, corrected QT, TSH, thyroid-stimulating; WBC, White blood cell; Y, year.*

In ROC analysis, the basal-CRP above 50.65 mg/L predicted the high risk of di-LQTc with 80% of sensitivity and 81.30% of specificity in Covid-19 patients, the area under the curve was 0.891 (95%CI: 0.806–0.976, p=0.004) shown in Figure1. Besides, mortality was observed due to respiratory failure in all dead Covid-19 patients.

Table 2. Baseline characteristics significantly associated with basal CRP.

Variable	r	p-value
Age	0.434	<0.001
BMI	0.390	<0.001
Length of hospital stay	0.509	<0.001
WBC	0.329	0.003
AST	0.384	<0.001
Glucose	0.335	0.002
Urea	0.391	<0.001
eGFR	-0.415	<0.001

Abbreviations: AST, Aspartate Aminotransferase; BMI, Body Mass Index; CRP, C-reactive protein; eGFR, estimated glomerular filtration rate; r, Spearman's rank correlation coefficient; WBC, White blood cell.

Table 3. Basal-CRP; Multivariate logistic regression analysis showing an independent predictor of di-LQTc in Covid-19 patients.

Variable	B	S.E.	Wald	df	p	OR	95% CI	
							Lower	Upper
Basal-CRP	0.031	0.015	4.081	1	0.043	1.031	1.001	1.062
BMI	0.010	0.007	1.874	1	0.171	1.010	0.996	1.023
Length of hospital stay	0.017	0.011	2.321	1	0.128	0.984	0.963	1.005
HT	0.245	0.756	2.712	1	0.100	0.288	0.065	1.267
DM	0.001	0.022	0.003	1	0.956	1.001	0.960	1.044
Age	0.540	0.784	0.474	1	0.491	1.715	0.369	7.973

Abbreviations: BMI, Body Mass Index; CI, confidence interval, CRP, C-reactive protein; di-LQTc, Drug-induced long corrected QT; DM, diabetes mellitus type 2; eGFR, estimated glomerular filtration rate; HT, hypertension; OR, odds ratio; SE, Standart Error.

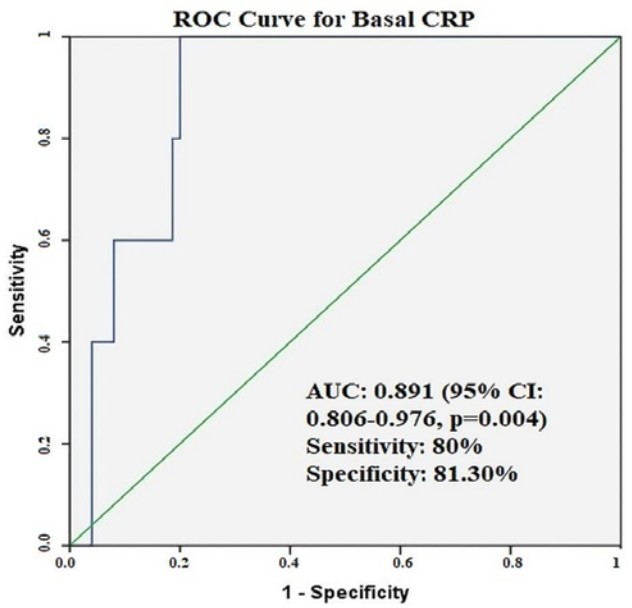

Figure 1. ROC curve for the specificity and sensitivity of basal-CRP. Abbreviations: AUC: area under the curve; CI, confidence interval; CRP, C-reactive protein; ROC, receiver operating characteristic curve.

Discussion

The main finding of this study was that COVID-19 patients with di-LQTc could be treated by adding metoprolol to the treatment protocol. Additionally, in our study, the high basal-CRP level was the independent predictor of di-LQTc in Covid-19 patients. We have shown that basal-CRP above 50.65 mg/L suggests the high risk of di-LQTc with 80% of sensitivity and 81.30% of specificity in Covid-19 patients.

According to the current literature reported in China, the overall mortality rates ranged from 1-15% due to Covid-19 (15). A recent study involving 5,700 patients in New York, USA, reported a 21% mortality rate in intensive care units (16). In this study, the in-hospital mortality rate was 3.125% (n=5). In our study in the metoprolol group, we have seen 1.92 fold lower mortality rates, but this finding was not statistically significant.

CRP is a positive acute-phase reactant that increases in all inflammatory processes especially in infections (4). We measured CRP to assess patients' response to Covid-19 infection. In the literature, there is evidence that increased age and high D-Dimer levels are the factors related to the mortality rates (17, 18). For instance, Ocak et al. found that age, CRP, and frontal QRS-T angle are independent predictors of Covid-19 disease severity (17). Our study also showed that a high basal-CRP level is an independent risk factor for di-LQTc rates. On admission, the values of basal CRP above 50.65 mg/L suggest a high risk of acquired di-LQTc. However, we did not find a relationship between di-LQTc and mortality.

Beta-blockers are currently used for the treatment of coronary artery disease and chronic heart failure (19). Metoprolol is one of the selective beta-1 blocker drugs and a lipophilic drug that reduces the heart rate, and It can be used to treat ventricular (VT) and supraventricular tachycardias. According to our current knowledge, in the early phase of the infection, patients typically show features as impaired myocardial functions, decreased vascular tone, and high cardiac output symptoms feature like tachycardia (20). With this situation, the diastolic functions begin to deteriorate in the later stages of the infection due to increased adrenergic drive detrimental over the myocardium (21-24). Also, in acute sepsis and septic shock, diastolic dysfunction is a good predictor for mortality as identified in recent meta-analyses (25,26). It is of vital importance in terms of protection of systolic and diastolic functions, regulation of cardiac output, and prevention of myocardial damage caused by the infective process. For that reason, we thought that we could benefit from beta-blockers, which commonly we have been using before. According to our knowledge, beta-1 blockade also showed improvements in patients with heart failure in diastolic functions (26). Additionally, beta 1-blockers reduce the workload on the heart by reducing the heart rate and decreasing the effects of sympathetic activity on the heart. A decrease in HR allows for improvement in ventricular filling during diastole, increase coronary perfusion, and increase cardiac output. Morelli et al. proposed that in septic patients, HR can be safely decreased without affecting organ perfusion (27). In patients with myocarditis and Takotsubo cardiomyopathy, successful use of beta-1 blockers has also been identified (28,29). In this study, we could control the heart rate, and

treat the di-LQTc by adding metoprolol tartrate to the treatment protocol in the metoprolol group.

A huge cascade of pro-and anti-inflammatory cytokines is caused by sepsis (4,30). Poor outcomes are associated with elevated levels of pro-inflammatory cytokines (TNF-alpha and IL-6) or their persistence in the serum (31). For example, TNF-α and IL-1β synergistically depress myocardial functions, and TNF-α induces insulin resistance (32,33). Interestingly, there appears to be a contrast between the activity of beta1 and beta2 receptors in modulating the cytokine storm. For instance, by modulating the cytokine profile, beta1-blockade and beta2-receptor activation may suppress the pro-inflammatory response (34). In previous studies proposed that beta1-blocker esmolol decreases TNF-a levels in the blood and intraperitoneal fluid in septic rats and preserves the function of the intestinal lymph node barrier (35,36) Also, landiolol, which is a beta1-blocker, decreases lung and serum levels of pro-inflammatory cytokines (37). Similarly, Ackland et al. proposed that metoprolol administration prior to the onset of endotoxemia, may reduce IL-6 and myocardial expression of cytokines that mediate cardiac dysfunction (38). In contrast to these findings, Calzavacca et al. found that atenolol infusion did not alter TNF-alpha and IL-6 levels (39). According to our knowledge so far, the blockade of beta2- receptors would increase TNF-α and IL-6, enhance inflammation, augment splenocyte apoptotic rate, decrease splenocyte proliferation, and augment granulocytes and pro-inflammatory monocytes (40). For that reason, non-selective blockers may disturb anti-inflammatory mechanisms. Also, the anti-inflammatory pathways are positively modulated in opposite directions by beta1- blockers. For example, by adding a selective beta1-blocker, we may increase IL-10 production which acts as an anti-inflammatory marker (39,41). Moreover, selective beta-1 blockers may decrease TNF-α and IL-6 levels (38-40). We thought that Covid-19 sepsis-associated myocardial instability may be favorably modulated by beta-1 blockers. More investigations are needed to understand whether selective beta1-blockers may provide benefits over the immune system is concerned.

Hydroxychloroquine and macrolides are shown to be associated with VT and TdP in various researches (22,23). Di-LQTc is associated with VT, which could be one of the causes of sudden cardiac death (21). In our study, we did not see any malignant arrhythmia in di-LQTc patients during Covid-19 treatment. According to our results, we believed that we could treat the di-LQTc by adding metoprolol. While a prophylactic metoprolol treatment for every patient who receives hydroxychloroquine is not required, but prophylactic therapy for high-risk patients with di-LQTc (>65 years Covid-19 patients with long QTc and who have comorbid risk factors such as diabetes, dyslipidemia, and arterial hypertension) may be lifesaving. The physicians should carefully assess the risks of hydroxychloroquine and other QT-prolonging drugs in the clinical evaluation of Covid-19 patients.

There are some limitations to our study. First, the main limitation of the present study is that the study was conducted with fairly small sample size. Although a multivariate model was conducted to adjust confounding variables, a bias was inevitable, since this was a single-center study. Multicenter trials with more patients could have better results and more data. Second, to assess long-term clinical results, a follow-up period of the in-hospital period may not be adequate. Third, whether this beneficial effect on di-LQTc is a general class effect of beta-1 selective group drugs or a special effect of metoprolol, we do not know. To generalize the results, we need to make studies with other beta-blocker drugs too. Fourth, hydroxychloroquine treatment was removed from the current guidelines. These factors are limiting our study.

Conclusion

In conclusion, this study demonstrated the beneficial effects of metoprolol tartrate in the treatment of di-LQTc in Covid-19 patients. Metoprolol tartrate may be considered in the therapy of di-LQTc, but to generalize these results large multi-center clinical trials are needed.

Ethical Approval: The study was approved by the Istanbul Yeni Yuzyil University Science, Social and Non-Interventional Health Sciences Research Ethics Committee (Number:2020/06-447), and The Republic of Turkey Ministry of Health sci-entific research platform (Number:2020-05-14T14_03_43).

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Concept: MH, GA, BH, AA
Literature Review: MH, GA, BH, AA
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Data acquisition: MH, GA, AA
Analysis and interpretation: MH, BH
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