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Impact of Adding Favipiravir to Hydroxychloroquine and Azithromycin Treatment on QTc Interval in COVID-19

Hidroksiklorokin ve Azitromisin Tedavisine Favipiravirin Eklenmesinin COVID-19'da QTc Aralığı Üzerindeki Etkisi

İdris Buğra ÇERİK[a], Hatun ÖZTÜRK ÇERİK[b], Ahmet DOĞAN[c], Seçkin DERELİ[d], Osman BEKTAŞ[d], Yasemin KAYA[e]

[a]Department of Cardiology, Sivas Cumhuriyet University Faculty of Medicine, Sivas, TURKEY
[b]Clinic of Infectious Diseases and Clinical Microbiology, Sivas Numune Hospital, Sivas, TURKEY
[c]Clinic of Infectious Diseases and Clinical Microbiology, Ordu State Hospital, Ordu, TURKEY
[d]Department of Cardiology, Ordu University Faculty of Medicine, Ordu, TURKEY
[e]Department of Internal Medicine, Ordu University Faculty of Medicine, Ordu, TURKEY

ABSTRACT Objective: The Coronavirus disease-2019 (COVID-19) pandemic has caused the death of many people worldwide. Treatment protocol had to be developed as soon as possible so drug combinations, whose reliability has not been fully disclosed, have started to be used. In this study, we aimed to evaluate the effect of azithromycin (AZT), hydroxychloroquine (HCQ), and favipiravir (FVR) combination on the corrected QT (QTc) interval. **Material and Methods:** Eighty-four consecutive COVID 19 patients were enrolled in the study. All patients received AZT and HCQ, however, FVR was added to the combination in 32 patients with severe pneumonia at the beginning. ECG characteristics of all patients before treatment and on the fifth day of treatment were compared. **Results:** There was no significant difference between the HCQ+AZT group (n=52) and HCQ+AZT+FVR groups (n=32) in terms of baseline clinical characteristics. QTc interval significantly prolonged on the fifth day of treatment in the HCQ+AZT group (413,75±30,13; 440,27±36,11 p<0.001) and in the HCQ+AZT+FVR group (426,65±32,83; 468,22±42,13 p<0.001). When both groups were compared in terms of ΔQTc, a significant increase was observed in the HCQ+AZT+FVR group compared to the HCQ+AZT group (40(-14/175), 23(-28/213) respectively, p=0.042). In seven of the patients, QTc> 500 ms was detected after the treatment, four patients in the HCQ+AZT+FVR group and three patients in the HCQ+AZT group. **Conclusion:** We observed that FVR caused more prolongation in the QTc interval when used with the combination of HCQ+AZT. We recommend that patients who receive this treatment be monitored more closely for QTc.

Keywords: Azithromycin; COVID-19; favipiravir; hydroxychloroquine; QT interval

ÖZET Amaç: Koronavirüs hastalığı-2019 [coronavirus disease-2019 (COVID-19)], dünya çapında birçok ölüme neden olan bir pandemiye yol açtı. Tedavi protokolünün bir an önce geliştirilmesi gerektiğinden, güvenilirliği tam olarak tanımlanmamış ilaç kombinasyonlarının kullanılmasına neden oldu. Bu çalışmada, azitromisin (AZT), hidroksiklorokin (HCQ) ve favipiravirin (FVR) kombinasyonunda düzeltilmiş QT (QTc) aralığı üzerindeki etkisini değerlendirmeyi amaçladık. **Gereç ve Yöntemler:** Çalışmaya, 84 ardışık COVID-19 hastası dâhil edildi. Tüm hastalara AZT ve HCQ verildi, ancak başlangıçta şiddetli pnömonili 32 hastada kombinasyona FVR eklendi. Tüm hastaların tedavi öncesi ve tedavinin 5. gününde elektrokardiyografi özellikleri karşılaştırıldı. **Bulgular:** HCQ+AZT grubu (n=52) ile HCQ+AZT+FVR grupları (n=32) arasında başlangıç klinik özellikleri açısından anlamlı fark yoktu. QTc aralığı, tedavinin 5. gününde HCQ+AZT grubunda (413,75±30,13 msn; 440,27±36,11 msn p<0,001) ve HCQ+AZT+FVR grubunda (426,65±32,83 msn; 468,22±42,13 msn p<0,001) anlamlı şekilde uzadı. Her 2 grup ΔQTc açısından karşılaştırıldığında, HCQ+AZT+FVR grubunda, HCQ+AZT grubuna göre anlamlı bir artış gözlendi (sırasıyla 40 (-14/175) msn, 23 (-28/213) msn, p=0,042). Tedaviden sonra hastaların 7'sinde QTc>500 msn ölçüldü, bu hastaların 4'ü HCQ+AZT+FVR grubunda ve 3'ü HCQ+AZT grubundaydı. **Sonuç:** Çalışmamızda, HCQ+AZT kombinasyonu ile kullanıldığında FVR'nin, QTc aralığında daha fazla uzamaya neden olduğunu gözlemledik. Bu tedaviyi alan hastaların, QTc için daha yakından izlenmesi gerektiği kanaatindeyiz.

Anahtar Kelimeler: Azitromisin; COVID-19; favipiravir; hidroksiklorokin; QTc aralığı

Correspondence: İdris Buğra ÇERİK
Department of Cardiology, Sivas Cumhuriyet University Faculty of Medicine, Sivas, TURKEY/TÜRKİYE
E-mail: cerikbugra@gmail.com

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The severe acute respiratory syndrome-coronavirus-2 (SARS-CoV-2) virus is the cause of coronavirus-2019 disease (COVID-19), which causes alarming worldwide due to its high mortality. Several drug treatments have been investigated since World Health Organization has declared it as a pandemic.

In the outbreak of COVID-19 pandemic, chloroquine and hydroxychloroquine (HCQ) have emerged as a potential therapeutic option for the treatment.[1] These drugs are widely used for COVID-19 in many countries.

Azithromycin (AZT) is a macrolide antibiotic which is widely used to treat respiratory tract infections.[2] The combination of AZT with HCQ has been shown to potentiate viral load reduction and disappearance.[3] In many countries, the combination of chloroquine/HCQ and AZT is used as standard therapy in the COVID-19 outbreak.

The common feature of these drugs is that they cause a long corrected QT (QTc) interval and have the potential for cardiac arrhythmia.[2,4] Although these drugs are used for a short time (5-10 days), it has been observed that QTc prolongation may require discontinuation of treatment in pandemic studies.[5-9] Likewise, significant arrhythmias were observed in patients hospitalized for COVID-19.[10] The arrhythmogenic effects of other drugs [e.g. favipiravir (FVR), lopinavir/ritonavir] that can be added to this treatment are also completely uncertain.

FVR is a RNA-dependent RNA polymerase inhibitor used for many RNA viruses.[11] It has been shown to provide faster viral clearance and higher improvement in chest imaging in patients with respiratory system involvement.[12] FVR is currently used in two countries for the potential efficacy in the COVID-19 outbreak.

The arrhythmogenic effect of adding FVR to chloroquine/HCQ and AZT is ambiguous. Studies evaluating the effects of FVR on QTc interval in the pre-pandemic period are contradictory.[13,14] In this study, we aimed to evaluate the effects of adding FVR to HCQ and AZT treatment on the QTc interval.

MATERIAL AND METHODS

A retrospective study was conducted between the dates of 23 May 2020 and 15 Jul 2020 for patients who received inpatient treatment due to COVID-19. Approval from the Ethics Committee of Ordu University was obtained (2020/146). The procedures used in this study adhere to the tenets of the Declaration of Helsinki. Because of the retrospective study design, the committee waived the requirement for informed patient consent. According to previous similar studies in the literature, as a result of the simulation analysis performed through PASS 11 (Power and Sample Size, version 11, for Windows), the sample size required for 80% power was determined as at least 34 individuals in total.

The study population is patients who are admitted to the emergency department because of their symptoms related to COVID-19 disease. SARS-CoV-2 RNA positive patients by real-time reverse transcription-PCR from the nasopharyngeal swab sample or patients with COVID-19 compatible involvement in chest computed tomography (CT) were included in the study. Patients not meeting the criteria for therapy were excluded from the study.

Medical treatment of patients was given according to local treatment guidelines for COVID-19. All patients received 200 mg bid HCQ (5 days) after loading 400 mg bid on the first day. AZT was loaded with 500 mg od on the first day and then was continued 250 mg od (5 days). FVR was given in patients with severe pneumonia, 1,600 mg bid was loaded on the first day and 600 mg bid continued (5 days).[15]

AZT and HCQ treatment was given to 52 patients with positive COVID-19 Polymerase Chain Reaction (PCR) test and defined as HCQ+AZT group. HCQ, AZT, and FVR treatment was given to 32 patients with positive COVID-19 PCR test and/or severe pneumonia on chest CT and defined as HCQ+AZT+FVR group. Electrocardiographic (ECG) features of these two groups were compared.

The treatments patients received for concomitant diseases and the use of antiarrhythmic drugs were recorded.

Peripheral venous blood samples of the patients were obtained on their admission to the inpatient ward and repeated daily. An automated blood cell counter (Beckman, California) was used for measuring complete blood count parameters. Blood biochemistry parameters were measured in terms of C-reactive protein, troponin, creatinine, liver transaminases, and serum electrolytes.

Serum electrolyte levels were monitored and noted as it may affect the QTc interval of all patients. If serum potassium <3.5 mmol/L, calcium level <9 mg/dL (2.2 mmol/L), magnesium level <1.5 mg/dL (<0.6 mmol/L), electrolyte replacement therapy was administered.

Twelve lead ECG was performed to all patients by the E70 12 channel ECG machine (Guangdong Biolight Meditech Co.) before and five days after treatment initiation. QRS duration, QRS morphology, and QT interval duration were recorded in all patients. The calculation of the QTc interval was made manually by a cardiologist blinded to the study using Bazett's formula. All ECG analyzes were performed by a single cardiologist. If a baseline bundle branch block (BBB) was present, the J-T interval was measured and 120 ms was added to obtain the QT interval duration.

Patients under 18 years old, patients with baseline QTc> 500 ms, patients using concomitant medication that prolongs QTc, and patients who were added FVR to treatment regimen after the first day were excluded from the study.

STATISTICAL ANALYSIS

In all statistical analyses, SPSS 22.0 Statistical Package Program for Windows (SPSS Inc., Chicago, IL, USA) was used. In order to test the normality of distribution, Kolmogorov-Smirnov test was used. The continuous variables were expressed as mean±standard deviation, the categorical variables as percentage. In order to test the difference of the numeric variables between the groups, Student t-test or Mann-Whitney U test was used. In order to test the difference of the categorical variables between the groups, chi-square test was used. The paired samples test was used to compare the parameters of electrocardiography before and after treatment. A p value of <0.05 was accepted as statistically significant.

RESULTS

When the patients in HCQ+AZT+FVR group and HCQ+AZT group were compared; were compared the age was higher (75.6±13.36; 65.13±19.79; respectively, p=0.02), lymphocyte was significantly lower (p=0.01) in the HCQ+AZT+FVR group. There was no difference in other parameters (Table 1).

When electrocardiographic parameters were compared between HCQ+AZT+FVR group and HCQ+AZT group; before treatment QRS (105.70± 23.17 ms and 95.06±20.42 ms; respectively), after treatment QRS (106.91±23.0 ms and 94.67±17.62 ms; respectively) and after treatment QTc (468.22± 42.13 ms and 440.27±36.11 ms; respectively) were significantly higher in the group HCQ+AZT+FVR (respectively; p=0.05 p=0.01, p=0.004) (Table 2).

When QRS and QTc before and after treatment were compared in both groups, only QTc was significantly higher in two groups (in HCQ+AZT+FVR group; before treatment QTc 426.65±32.83 ms after treatment QTc=468.22±42.13 ms p<0.001 in HCQ+AZT group; before treatment QTc=413.75± 30.13 ms after treatment QTc=440.27±36.11 ms p<0.001) (Table 3).

When **Δ**QRS and **Δ**QTc were compared, there was no significant difference between the groups in **Δ**QRS and there was a significant difference between the groups in **Δ**QTc (in HCQ+AZT+FVR group 40 (-14/175) ms and in HCQ+AZT group 23 (-28/213) ms p=0.042) (Table 4) (Figure 1).

In seven of the COVID-19 patients included in the study, QTc>500 ms after treatment was detected in four patients in the HCQ+AZT+FVR group, and three patients in the HCQ+AZT group. Characteristics of patients with QTc>500 ms according to treatment groups are given in Table 5.

In patients included in the study; no new-onset atrial fibrillation, ventricular tachycardia, Torsade de Pointes, and arrhythmogenic death were observed.

DISCUSSION

This study shows that HCQ and AZT cause significant prolongation in the QTc interval, even with short-term use. Adding FVR to AZT and HCQ causes

TABLE 1: Comparison of baseline characteristics and laboratory findings of COVID-19 patients using and not using favipiravir.

Variables	HCQ+AZT+FVR group n=32	HCQ+AZT group n=52	p value
Age, years	75.6±13.36	65.13±19.79	**0.02**
Gender, male, n (%)	19 (59.37)	25 (48.07)	0.30
Hypertension, n (%)	22 (68.75)	31(59.61)	0.16
Diabetes mellitus, n (%)	12 (37.5)	11(21.15)	0.12
Coronary artery disease, n (%)	7 (21,18)	15 (28.84)	0.58
Heart failure, n (%)	10 (31,25)	12 (23.07)	0.26
Hemoglobin, g/dL	11.86±3.44	12.38±2.14	0.43
White blood cell, 10^3 uL	11.73±7.27	9.93±5.05	0.23
Neutrophil, 10^3 uL	9.05±6.31	7.26±4.80	0.19
Lymphocyte, 10^3 uL	1.15±0.67	1.78±1.07	**0.01**
Monocyte, 10^3 uL	0.78±0.37	0.69±0.34	0.33
Platelet, 10^3 uL	226.86±111.77	241.73±75.35	0.51
Mean platelet volume,	10.31±1.31	10.49±1.02	0.54
Creatinin, mg/dL	1.69±1.75	1.54±2.13	0.77
GFR, mL/dk/1.73 m^2	52.88±32.63	61.22±35.63	0.35
Sodium, mEq/L	135.05±7.87	137.69±6.16	0.13
Potassium, mmol/L	4.19±0.71	4.13±0.64	0.75
Calcium, mg/dL	8.92±0.42	9.10±0.56	0.18
Albumin,	3.51±1.41	3.86±0.56	0.10
Troponin	0.86±2.74	1.04±4.34	0.85
CRP	9.89±8.40	6.80±9.05	0.17

HCQ: Hydroxychloroquine; AZT: Azithromycin; FVR: Favipiravir; GFR: Glomerular filtration rate; CRP: C-reactive protein.

TABLE 2: Comparison of electrocardiography parameters of COVID-19 patients using and not using favipiravir.

Variables	HCQ+AZT+FVR group n=32	HCQ+AZT group n=52	p value
Heart rate, beats/minute	90.78±19.08	82.81±19.29	0.10
PR, ms	170±24.69	159.51±26.83	0.17
Before treatment QRS, ms	105.70±23.17	95.06±20.42	**0.05**
After treatment QRS, ms	106.91±23.0	94.67±17.62	**0.01**
Before treatment QTc, ms	426.65±32.83	413±30.16	0.10
After treatment QTc, ms	468.22±42.13	440.27±36.11	**0.004**

HCQ: Hydroxychloroquine; AZT: Azithromycin; FVR: Favipiravir; CRP: C-reactive protein; QTc: Corrected QT.

more prolongation in the QTc interval. Premature discontinuation of treatment due to long QTc was not needed and no arrhythmogenic event due to treatment was observed.

SARS-CoV-2 is a virus from the coronaviridae family, which is the cause of COVID-19 disease.[16] Treatment protocol had to be developed as soon as possible so drug combinations, whose reliability has not been fully disclosed, have started to be used. In many countries, various drugs are used in addition to the combination of HCQ and AZT, such as lopinavir/ritonavir, FVR, remdesivir.[17-19] In this

TABLE 3: Comparison of the parameters of electrocardiography before and after treatment.

	HCQ+AZT+FVR group n=32		
Variables	**Before**	**After**	**p value**
QRS, ms	105.70±23.17	106.91±23.0	0.21
QTc, ms	426.65±32.83	468.22±42.13	**<0.001**
	HCQ+AZT group n=52		
	Before	**After**	**p value**
QRS, ms	95.06±20.42	94.58±17.37	0.61
QTc, ms	413.75±30.13	440.27±36.11	**<0.001**

HCQ: Hydroxychloroquine; AZT: Azithromycin; FVR: Favipiravir; CRP: C-reactive protein; QTc: Corrected QT.

TABLE 4: Comparison of ΔQTc and ΔQRS.

	HCQ+AZT+FVR group n=32	HCQ+AZT group n=52	p value
Δ QTc median	40	23	0.042
(minimum/maximum)	(-14/175)	(-28/213)	
Δ QRS median	1.0	1.0	0.77
(minimum/maximum)	(-5/12)	(-38/14)	

HCQ: Hydroxychloroquine; AZT: Azithromycin; FVR: Favipiravir; CRP: C-reactive protein; QTc: Corrected QT; Δ= Delta; Min: Minimum; Max: Maximum.

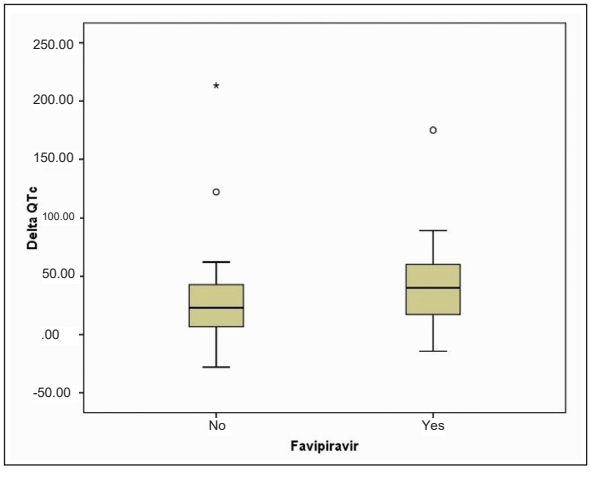

FIGURE 1: Delta corrected QT values according to groups.

study, we investigated the effect of AZT, HCQ, and FVR combination on the ECG characteristics to give the treatment in safer conditions.

HCQ and chloroquine are agents used in rheumatic diseases and malaria. In a study, Gautret et al. reported that HCQ potentiates viral load reduction and disappearance.[3] Chloroquine affects the action potential through the potassium channels and may cause QRS widening and QT interval prolongation.[20] Malign ventricular arrhythmias related to short-term chloroquine use during the COVID-19 outbreak have not yet been reported, nevertheless, it has been shown to cause >500 ms QTc interval and 35 ms ec prolongation in the average QTc interval.[5] HCQ may have less toxicity than chloroquine but is not without risk.[21] Previous studies with HCQ have been shown to cause high doses of ventricular arrhythmias and Torsades de Pointes (TdP).[22,23] In a recent study in COVID-19 patients, prolongation in QTc interval was also detected in short-term use in a patient group where HCQ and chloroquine were evaluated together.[9] However, the effect of short-term HCQ use on the QTc interval is uncertain.

AZT is an antibiotic which is used to treat respiratory tract infections. AZT-induced QT prolongation was especially observed in patients with concomitant use of other QT-prolonging drugs or patients with preexisting cardiovascular conditions.[2] The synergistic effect of HCQ and AZT has been shown in a study. So combination use was preferred in many countries.[3] In a study of COVID-19 patients treated with HCQ and AZT, an average increase of 19.3 ms in the QTc interval was observed. In the results of this study, it was observed that the combination use of HCQ and AZT did not cause a significant increase in the QTc interval compared to the use of HCQ alone, however, the maximum QTc interval is significantly higher in the combination group.[9] In our study, all patients used with HCQ and AZT in combination therefore the study population consisted of patients with a higher risk of QTc interval prolongation. In this study, a median 23 ms prolongation in the QTc interval was observed in the HCQ+AZT group, this value seems to be compatible with that in similar studies.

FVR is an RNA-dependent RNA polymerase inhibitor used for many RNA viruses. Its effectiveness has been previously shown in influenza viruses, arenaviruses, hantaviruses, flaviviruses, and enteroviruses.[11] SARS-CoV-2 is an RNA virus, like other viruses where FVR is effective. FVR has been shown to provide faster viral clearance and

TABLE 5: Characteristics of patients with QTc> 500 ms.

	QTc> 500 ms in HCQ+AZT+FVR group n=4	QTc>500 ms in HCQ+AZT group n=3
Male, n (%)	2 (50%)	1 (33%)
Age	67±14.67	80±4
Hypertension, n (%)	3 (75%)	2 (66.66%)
Diabetes mellitus, n (%)	1 (25%)	1 (33.33%)
Chronic renal failure, n(%)	3 (75%)	1 (33.33%)
Coronary artery disease, n (%)	2 (50%)	2 (66.66%)
Heart failure, n (%)	2 (50%)	1 (33.33%)
Baseline QTc, ms	446.50±54.69	453.0±51.06
After treatment QTc, ms	553.75±13.37	540.33±60.38

HCQ: Hydroxychloroquine; AZT: Azithromycin; FVR: Favipiravir; QTc: Corrected QT; CRP: C-reactive protein.

higher improvement in chest imaging in patients with respiratory system involvement.[12] Kumagai et al. showed that there was no significant increase in the QTc interval after administration of FVR 1,200 mg and 2,400 mg on 56 healthy volunteers.[14] However, Chinello et al. reported 98 ms ec prolongation in QTc interval due to FVR in a patient infected with ebolavirus. It was observed that QTc returned to normal after discontinuation of FVR in this patient.[13] Cardiac safety of FVR is uncertain in the COVID-19 patient group taking two risky drugs (HCQ and AZT) for prolongation in the QTc interval.

To the best of our knowledge, our study is the first to evaluate the cardiac safety of adding FVR to the combination of HCQ and AZT. Although the number of patients in this study is limited, a significant prolongation in the QTc interval was detected in the patient group receiving FVR treatment compared to the other group. Despite this prolongation, no patient had the medications discontinued prematurely because of long QTc interval. Torsades de Pointes or sudden cardiac death due to QTc prolongation were not observed in patients included in the study, however, this may be due to relatively small number of patients. It has been shown that 50 ms prolongation in QT interval is associated with two-fold increased all-cause mortality in patients with rheumatoid arthritis.[24] The frequencies of arrhythmia and arrhythmogenic death in COVID-19 disease should be clearly demonstrated in further large-scale studies.

It is recommended to discontinue treatment if QTc>500 ms, because it was associated with two or three times increased frequency of TdP.[25-27] In this study, we detected not only a marginally significant increase in median QTc with FVR, but also the QT interval >500 ms was in 4 patients in the patient group receiving FVR treatment, while the QT interval >500 ms was in 3 patients in the other group. The more prolongation in the QTc interval in the FVR group may be due to the direct effect of FVR on QTc interval as well as undefined drug interactions, however, the study cannot determine the reason for this. This suggests that FVR treatment should be given much more carefully in patients with a tendency to QT prolongation.

LIMITATIONS

There are several limitations in our study. Firstly, although the number of patients enrolled in the study is equivalent to similar studies, it may not be sufficient to assess the real frequency of arrhythmogenic events.[5] Second, our study was designed retrospectively. Third, the patients' diseases that existed before the COVID-19 infection were known, however, an echocardiographic evaluation was not routinely performed to the patients.

CONCLUSION

To the best of our knowledge, our study is the first to evaluate the cardiac safety of FVR in COVID-19 disease. We observed that FVR caused more prolongation in the QTc interval when used with the combination of HCQ+AZT. We also observed that the risky QT interval for arrhythmias such as TdP was higher in these patients. Although no arrhythmogenic event due to FVR was observed, we recommend that these patients should be monitored more closely for the QT interval.

Source of Finance

During this study, no financial or spiritual support was received neither from any pharmaceutical company that has a direct connection with the research subject, nor from a company that provides or produces medical instruments and materials which may negatively affect the evaluation process of this study.

Conflict of Interest

No conflicts of interest between the authors and / or family members of the scientific and medical committee members or members of the potential conflicts of interest, counseling, expertise, working conditions, share holding and similar situations in any firm.

Authorship Contributions

Idea/Concept: *İdris Buğra Çerik;* ***Design:*** *İdris Buğra Çerik;* ***Control/Supervision:*** *Osman Bektaş;* ***Data Collection and/or Processing:*** *Hatun Öztürk Çerik, Ahmet Doğan, Seçkin Dereli;* ***Analysis and/or Interpretation:*** *Yasemin Kaya;* ***Literature Review:*** *Hatun Öztürk Çerik;* ***Writing the Article:*** *İdris Buğra Çerik;* ***Critical Review:*** *Ahmet Doğan, Seçkin Dereli.*

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