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Effects of hydroxychloroquine and azithromycin use on ECG parameters due to COVID-19 in pediatric patient population

Pediatrik hasta popülasyonunda COVİD-19 sebebiyle hidroksiklorokin ve azitromisin kullanımın EKG parametreleri üzerine etkileri

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Abstract

Aim: Due to COVID-19 infection, the use of two drugs, hydroxychloroquine and azithromycin, with a high potential for arrhythmia, came to the fore in the pediatric patient group at the beginning of 2020, during the search for treatment. The aim is to reveal the synergistic arrhythmic effects of these two drugs in prolonging the QT interval on the ECG.

Materials and Methods: First of all, patients taking hydroxychloroquine were identified. Demographic data of these patients were recorded. In addition to hydroxychloroquine, azithromycin and other treatments they used were also recorded. Those with ECG data were selected. Transmyocardial repolarization parameters calculated by ECG were calculated retrospectively (QT, QTc, Tpe, Tpe/QT, Tpe/QTc). Then, laboratory findings and radiological imaging of these patients were recorded.

Results: Twenty-three pediatric patients who met the study criteria were identified. All of the patients were asymptomatic or mild disease. When initial and post-drug ECG parameters were compared; It was observed that the drugs did not have a significant arrhythmogenic effect on ECG parameters, especially QT interval and QTc.

Conclusion: Unlike the literature showing arrhythmic effects of these drugs in adult COVID-19 disease, hydroxychloroquine and azithromycin did not show such an effect in the pediatric population.

Keywords: COVID-19; ECG; QTc; Pediatrics; Arrhythmia.

Öz

Amaç: COVID-19 enfeksiyonu nedeniyle, 2020 yılının başında tedavi arayışı sırasında aritmi potansiyeli yüksek hidroksiklorokin ve azitromisin isimli iki ilacın kullanımı pediatrik hasta grubunda gündeme geldi. Amaç bu iki ilacın EKG üzerinde QT intervalini uzatmadaki sinerjistik aritmik etkilerini ortaya koymaktır.

Gereç ve yöntem: Öncelikle hidroksiklorokin alan hastalar tespit edildi. Bu hastaların demografik verileri kaydedildi. Hidroksiklorokine ilaveten kullandıkları azitromisin ve diğer tedavileri de kayıt altına alındı. EKG verileri olanlar seçildi. EKG ile hesaplanan transmiyokardiyal repolarizasyon parametreleri retrospektif olarak (QT, QTc, Tpe Tpe/QT, Tpe/QTc) hesaplandı. Ardından bu hastaların laboratuvar bulguları ve radyolojik görüntülemeleri kaydedildi.

Bulgular: Çalışma kriterlerine uygun 23 pediatrik hasta tespit edildi. Hastaların tamamı asemptomatik ya da hafif hastalık tablosundaydı. Başlangıç ve ilaç sonrası EKG parametreleri karşılaştırıldığında; başta QT intervali ve QTc olmak üzere EKG parametreleri üzerine ilaçların belirgin bir aritmojenik etkisi olmadığı görüldü.

Sonuç: Erişkin COVİD-19 hastalığında bu ilaçların aritmik etkilerini gösteren literatüründen farklı olarak, hidroksiklorokin ve azitromisin böyle bir etkiyi pediatrik popülasyonda göstermediler.

Anahtar kelimeler: COVİD-19; EKG; QTc; Pediatri; Aritmi.

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Introduction

COVID-19 infection has been a rapidly spreading infection worldwide since the beginning of 2020, and with its acceptance as a pandemic, various treatments have been sought. Treatments for COVID-19 infection in the early stages of the pandemic, either chloroquine (CQ) and hydroxychloroquine (HCQ) alone or in combination with azithromycin (AZT), have been recommended. CQ and HCQ are used in chronic inflammatory diseases such as rheumatoid arthritis and systemic lupus erythromatosus. It has been suggested that it could potentially inhibit virus entry into cells, particularly via the endosomal pathway, by inhibiting glycosylation of host receptors, proteolytic processing, and endosomal acidification in COVID-19 infection.[1]

These drugs, when used alone or in combination with AZT, can prolong the QT interval (QT) pathologically due to genetic or acquired reasons and cause malignant ventricular arrhythmias. Evaluation of QT and corrected QT (QTc) in electrocardiography (ECG) examination is important to reduce and prevent drug-related mortality and morbidity. Indiscriminate use may produce malignant arrhythmias such as “torsades de pointes” or ventricular fibrillation as a result of drug-induced long QT.

CQ and HCQ are drugs included in the aminoquinoline group. They prolong the QT by inhibiting voltage-gated sodium and potassium channels. The most important known side effects are QT prolongation and malignant ventricular arrhythmia. HCQ; It inhibits this channel by binding to the K channel protein, product of the KCNH2 gene. It results in prolongation of repolarization. In cases of congenital long QT, hypokalemia and hypomagnasemia where repolarization is prolonged; It constitutes an important risk factor for severe ventricular arrhythmia, “torsades de pointes”.[2] Inducible risk factors were stated in another study as hypocalcemia, hypokalemia, hypomagnesemia, use of drugs that prolong QT.[3] Use of more than one drug that prolongs QT at the same time increases the risk of arrhythmias.

Adverse cardiovascular side effects have been described, especially in adults.[4] SARS Cov 2 virus, which is the cause of COVID-19, uses the ACE 2 receptor to enter the cell.[4] This receptor is a regulator of two opposite pathways of angiotensin 2 in the renin angiotensin system. The ACE 2 receptor has important cardiac functions. These; It can be listed as a negative regulator on myocardial hypertrophy, fibrosis and diastolic dysfunction. SARS Cov 2 is assumed to cause damage to the heart as well as the respiratory tract via the ACE 2 receptor. The ACE-Angiotensin-II-AT1R axis has been suggested to be the likely mechanism of more severe SARS Cov 2 infection. Stimulation of this axis triggers inflammation, thrombosis, fibrosis, and vasoconstriction.[5]

Acute infection in the pediatric population showed a milder course than the adult population. However, the effects of the COVID-19 infection appeared after the acute period. Kawasaki-like disease in the pediatric age group caused a group of hyperinflammatory diseases called MIS-C in the adolescent age group. These diseases, with their adverse cardiovascular effects, appeared on average 4-6 weeks after the transmission of the infection.

However, there is a potential for arrhythmia in the acute phase of COVID-19 infection. The prevalence of arrhythmia in hospitalized children was 5.5%.[6] This prevalence is the prevalence of the disease itself, regardless of the drug. An increase in the prevalence of arrhythmia can be predicted if drugs that prolong the QT, such as HCQ and AZT, are used.

Pharmacological form: HCQ: Hydroxychloroquine sulfate is produced as 200 mg tablets. The drug has a long half-life. The mean duration has been reported to be 20 days. In case of high dose use in a short time, it can lead to a cumulative toxicity.

AZT: It is a macrolide antibiotic. It has been used in treatment because of its antiviral activity. After entering the cell, it achieves this effect by alkalizing the inside of the cell. It prevents viral phagocytosis through the endosome. Because AZT prolongs QTc, there

is the potential for ventricular arrhythmias such as “torsades de pointes”.

Literature on HCQ use in childhood; mostly consists of adult case series. There is a modest literature on childhood. There is little research in the pediatric literature regarding the electrophysiological effects of HCQ and CQ use over a therapeutic dosage range. We present the data we have obtained in this area to the attention of the reader.

The study investigates the effects of asymptomatic and mildly symptomatic COVID-19 infection on transmyocardial repolarization parameters (QT, QTc, Tpe, Tpe/QT, Tpe/QTc parameters ventricular repolarization parameters) in children receiving HCQ therapy. In this way, we aimed to analyze the data in the group that does not require intensive care follow-up in case of mild disease.

Materials and Methods

Type of research

This study was carried out with the permission of the Turkish Ministry of Health. The study was carried out in a third step hospital, which is the only reference hospital of the city. This is a retrospective cohort study of pediatric patients (0-18 years) using HCQ alone and/or combination therapy with AZT for the treatment of COVID-19 between March 28, 2020 and May 25, 2020.

Study population (research universe)

In our hospital, the diagnosis of COVID-19 was confirmed by PCR tests studied from nasopharyngeal and oropharyngeal swab samples from all patients. ECG monitoring was performed daily in accordance with the drug protocol. Liver kidney functions and electrolytes were also monitored. The patients were hospitalized and did not require organ support treatment.

As a result of the archive scanning, a total of 42 patients who received HCQ treatment were identified among the patients diagnosed with COVID-19. In the archive records, patients with daily ECG follow-ups at the beginning and after the hospitalization were selected. A total of 26 patients were identified. While at least two ECGs were evaluated, those with a minimum of 3 days between the ECG recording dates were included in the study. Three patients with missing ECG data were excluded from the study. ECG data of 23 patients were obtained.

Exclusion criteria:

- Patients without initial ECG in their follow-up. Patients who had an ECG at the beginning but did not have an ECG on the 3rd day at least, and patients who did not complete the requirement to complete ECG examinations at the end of the treatment,
- Patients with QTc>470 millisecond (msec) in initial investigations,
- Patients with central cyanosis and dyspnea; patients with oxygen-free saturation <92%
- Patients requiring intensive care follow-up

Medication dosage: HCQ dose: It was given in accordance with the Turkish Ministry of Health guidelines. [7] On day 1 of treatment: 6,5 mg/kg dose (maximum dose 400 mg) was given twice daily. On days 2-5, half of this dose (maximum dose 200 mg) was given 2 times a day.

AZT dosage: 10 mg/kg once daily (maximum dose 500 mg) on day 1 in children older than 6 months. On days 2-5, a dose of 5 mg/kg was given once a day (maximum dose 250 mg).

Data collection tools

Age, gender, admission complaint, history of comorbid disease, treatments used were recorded as demographic parameters. Laboratory results were scanned. Complete blood count, liver-kidney function tests, electrolyte measurements, enzymes showing cardiac damage were listed as parameters. Radiological records (lung x-rays and thorax computed tomography) were evaluated by the pediatric infectious disease physician. In order to evaluate cardiotoxicity, QRS duration, QT, QTc, Tpe, Tpe/QT, Tpe/QTc parameters measured in ECG were measured by a pediatric cardiologist.

ECG recordings were performed using Nihon Kohden Cardiofax S device with 25 mm/sec and 10 mm/mV 12 leads. QT is the

time between the onset of activation and the end of its repolarization of the ventricular myocardium, represented by the onset of the QRS and the end of the T wave, respectively. The measurement was made in lead II and V5 or V6 with the longest measured value. The heart rate corrected QT (QTc) interval was calculated using Bazett's formula (QT/√R-R). As a general reference, patients with a prolonged resting QTc of ≥ 470 ms, regardless of cause (congenital or acquired), were considered a risk marker for "torsades de pointes" or ventricular fibrillation. Tpe; It was calculated as the time interval between the peak value of the T wave and the end of the t wave.

Echocardiography was not performed in our patients due to the risk of contamination.

Among the laboratory parameters, hypokalemia, hypomagnesemia and various factors that could prolong QT and QTc were taken into consideration. Inducible risk factors were defined as hypocalcemia, hypokalemia, and hypomagnesemia.

Among the treatment options, it was observed that many patients received additional treatments, especially AZT, in addition to HCQ treatment.

Analysis of data

Parametric numerical values were expressed as mean±standard deviation. Age, platelet, lymphocyte count, polymorphonuclear lymphocyte, urea, AST, ALT, albümin, total protein, alkaline phosphatase, lactate dehydrogenase (LDH), INR, aPTT, Troponin I, fibrinogen and electrolytes were laboratory parameters with a statistically normal distribution. All ECG numerical parameters showed a statistically normal distribution. Student`s t-test was used to compare variables. Chi-square test was used for categorical variables. p value <0.05 was considered statistically significant. Pearson correlation analysis was used.

Ethics comittee Approval

Our study was carried out in accordance with the Declaration of Helsinki Principles. Our study was approved by the local ethics committee (Ethics Committee Approval Date and Number: 2020: 8/11)

Results

Between March 28, 2020 and May 25, 2020, a total of 23 patients, 9 boys (40%) and 14 girls (60%) who used HCQ therapy and whose ECG follow-up were performed, were identified (Table 1). The mean age was 13.3±2.8 years.

Most of the patients did not have a comorbid disease. One patient was receiving epilepsy treatment, and one patient had Down syndrome. Asymptomatic patients were 22%. The most common symptom was cough (26%). Chest radiography consistent with viral pneumonia was seen in 26%. Chest X-ray was evaluated as normal in 17% of the patients. All patients were using HCQ. The number of patients who received the combination with AZT was 5. Patients receiving triple therapy in combination with AZT and oseltamivir comprised 52% of the entire study population (Table 1).

Numerical laboratory parameters such as hemoglobin, white blood cell count (WBC), GGT, D-dimer, ferritin, creatine kinase (CK), creatine kinase-myocardial band (CK-MB) and lactate values were parameters that did not show a statistically normal distribution (Table 2). These parameters were expressed in the Table 2 with min-max values, unlike other parameters. All ECG measurements and other laboratory parameters showed statistically normal distribution. These parameters are included in the Table 2 with their mean and standard deviation values.

WBC, neutrophil, lymphocyte and hemogram numerical values obtained from the patients were recorded to be within normal laboratory values.

Parameters showing cardiac damage: Cardiac Troponin I, CK-MB and D-dimer values were recorded within normal ranges.

Calcium, magnesium, potassium and sodium values were found to be normal in the evaluation in terms of inducible risk factors.

Table 1. Summary of pediatric COVID-19 infections characteristics.

Parameters		**Patients**	
		Number/n	**Percent /%**
Gender	Girl	14	60
	Boy	9	40
Complaint	None	5	22
	Weakness	4	18
	Fever and headache	5	22
	Cough	6	26
	Diarrhea vomiting	1	4
	Facial paralysis	1	4
	Sensory Loss	1	4
Comorbid Condition	None	21	92
	Epilepsy	1	4
	Down syndrome	1	4
Lung X-ray	Normal	4	17
	Mild infiltration	6	31
	Paracardiac infiltration	**7**	26
	Compatible with viral pneumonia	**7**	26
Torax BT	None	11	48
	Normal	5	22
	Ground glass densities of viral pneumonia	7	30
Treatment	HCQ	2	9
	HCQ+ AZT	5	22
	HCQ+ AZT +Oseltamivir	12	52
	HCQ+ Acyclovir	1	5
	HCQ+ Favipavir	3	12

Table 2. Summary of pediatric COVID-19 infections demographic and laboratory findings.

Numeric parameter	**n**	**Mean**	**Standard deviation (±)**
Age (years)	23	13.3	2.8
Platelet ($x10^3$)	23	247.4	72.1
Lymphocyte Count ($x10^3$)	23	1892.8	636
Polymorphonuclear lymphocyte ($x10^3$)	23	3660.6	2021.4
Urea (mg/dl)	23	20.5	4.9
AST (U/L)	23	19.8	5
ALT (U/L)	23	16.1	5
Albumin (g/L)	23	4	0.4
Total Protein (g/L)	10	7.6	0.4
Alkaline Phosphatase (U/L)	22	179.4	84.5
LDH (U/L)	23	215.5	74.8
INR	21	1.1	0.4
aPTT (sec)	21	30.1	4.1
Troponin I (ng/L)	22	0.01	0
Fibrinogen (mg/dl)	22	317.3	139.1
Sodium (mmol/lt)	23	139.4	3
Potassium (mmol/lt)	23	4.2	0.4
Calcium (mg/dl)	23	9.3	0.7
Magnesium (mg/dl)	14	2	0.1
Numeric parameter	**n**	**Min**	**Max**
Hemoglobin (g/dl)	23	9.2	15.9
WBC	23	2745	11440
GGT (U/L)	23	7	66
D-dimer (ng/ml)	22	84	3620
Ferritin (µg/L)	21	5.4	405
CK (µg/L)	22	29	194
CK-MB (µg/L)	21	2	13.1
Lactat (mg/dl)	16	0.9	374

While there were 2 patients who received HCQ treatment alone, combination therapy was used in the other 21 patients. (Table 1). Only one patient had a QTc value of 450 msec after HCQ treatment. None of the patients required inotropic therapy. No patient developed ventricular arrhythmias or "torsades de pointes" with treatment. All patients were in sinus rhythm.

A 20 msec prolongation of the QT was noted at the next value after drug use compared to the baseline value. No significant prolongation was observed in QTc measurements. No difference was observed between Tpe values. A statistical difference in Tpe/QT ratio was recorded in the measurements of Tpe/QT and Tpe/QTc. However, this difference was not clinically significant (Table 3). In addition, the last QTc value was detected as 400 msec in the epilepsy patient using levatiracetam.

Table 3. Summary of pediatric COVID-19 infections ECG findings.

ECG parametrers	n	Mean	Standard deviation (±)	*p* value
QT baseline value	23	354 (msec)	29.2	**QT baseline value - QT final value: 0.012**
QT final value	23	374.4 (msec)	26.3	
QTc baseline value	23	411.4 (msec)	16.6	QTc baseline value-QTc final value : 0.354
QTc final value	23	414.8 (msec)	17.9	
Tpe first value	23	70 (msec)	9.4	Tpe fisrt value- Tpe last value 0.464
Tpe last value	23	68.1 (msec)	8.9	
Tpe/QT first value	23	0.19	0.027	**Tpe/QT first value- Tpe/QT last value: 0.02**
Tpe/QT final value	23	0.18	0.026	
Tpe/QTc first value	23	0.17	0.02	Tpe/QTc first value- Tpe/QTc last value: 0.372
Tpe/QTc final value	23	0.16	0.01	

Discussion

This study aims to examine the reliability of the combined use of HCQ and AZT; planned to determine arrhythmia potentials.

The ratio of asymptomatic patients to the patient population in our study is similar to that in larger series.[8]

T wave shows ventricular repolarization. Transmyocardial parameters are measurements based on the T wave. Measurement of these parameters indicates the risk of ventricular arrhythmia. These parameters are: Tpe, QT, QTc, Tpe/QT and Tpe/QT. Transmyocardial repolarization parameters including Tpe, QT interval, QTc, and Tpe/QT ratio have been reported to be associated with increased risk of cardiac arrhythmia.[9]

A study by Ece et al. included a population of pediatric patients infected with COVID-19.[9] Patients not taking QT prolonging drugs were included. The arrhythmia potential of the COVID-19 infection itself was evaluated. QT and QTc dispersions Tpe parameters were found to be significantly higher in the patient group compared to the healthy pediatric population. This study suggested that with the disease itself, drugs such as HCQ and AZT to be used to treat would increase the potential for arrhythmia.

Arrhythmia has been documented with short-term use of high-dose HCQ in patients diagnosed with critical COVID-19 infection in the adult review.[10] Risk reduction strategies for arrhythmia by ECG monitoring have been recommended in all patients. Although ECG monitoring is helpful in preventing "torsades de pointes", post-baseline ECG monitoring in pediatric patients was unnecessary in terms of reducing exposure to infected patients in repeated follow-ups. Although QT prolongation is statistically significant in studies, clinical arrhythmia is extremely rare, as reported in many other studies.

Timing of QTc prolongation; A study reported that QTc prolongation was recorded maximum 3-4 days after starting HCQ and AZT drugs.[11] In our study, the minimum period between ECG recording dates was 3 days, which coincided with the period specified in the mentioned article. In this way, we evaluated the potential for ventricular arrhythmias. We calculated the prolongation in QT and QTc.

Effects of antimalarial use on the cardiovascular system: In a meta-analysis review conducted in 2018, no side effects were found in the evaluation of cardiovascular side effects in patients using antimalarial therapy (mostly young).[12] In that review, we see that there are 7 studies of children using CQ. In these, most of the children did not have comorbid disease except malaria.

Factors determining QT prolongation differ from adults: The most important determinant of risk in patients with QT prolongation has been shown to be severe COVID-19 infection and use of QT prolonging drugs for adult patients. Our study targeted a population of less sick children who did not require intensive care monitoring. Studies were conducted in adults with severe disease under the influence of a cytokine storm or myocarditis. Receptors to which SARS Cov 2 binds in adult patients cause a different course than children. In underlying comorbid conditions such as diabetes, obesity and chronic lung disease, the behavior of this pathway changes in adults, leading to a severe course of the disease in adults. The disease is mild in children. Our patient group consists of cases with asymptomatic or mild disease. A possible risk factor for QT prolongation in our study is drug use. However, no significant QT prolongation was found in our study results. Another inducible risk factor in adult studies is electrolyte abnormalities. [13] In our study, there was no patient with severe electrolyte problems. The susceptibility to electrolyte problems is higher in adults. Electrolyte abnormalities can also be seen with renal effects and hyperinflammation-cytokine storm through the receptor to which SARS Cov 2 binds.[5]

Studies by the amount of QT prolongation: There are reviews reporting that the use of AZT and HCQ prolongs the QT and QTc by 40-60 msec.[14] In our study, unlike the literature, we did not detect any obvious QT and QTc prolongation in any group. In a study conducted in the healthy group, the drug alone prolonged the QTc by an average of 16 msec.[15] This finding is consistent with our study. No significant prolongation was recorded even in combination with other drugs in the case that did not require intensive care follow-up.

In a retrospective population study, it was reported that the combined use of HCQ and AZT increases cardiovascular morbidity and reveals the potential for heart failure.[16] In this study, which included a very large population, it was determined that the use of HCQ in combination with amoxocillin or sulfasalazine had no effect on cardiovascular mortality. This study shows that adverse side effects occur synergistically with the use of the two drugs. In our study, 52% of the patients used this combination. We did not find any significant arrhythmia potential among our findings in the smaller patient population without inducible risk factors.

In a meta-analysis of the combination of HCQ with AZT, the drug itself was shown to be effective in increasing the QTc above 500 msec.[17] It is also reported in this study that the incidence of arrhythmia is lower than previously stated. In order to make a similar observation in our study, we excluded patients with QT>470 msec on initial ECG. At the same time, there was no patient with QT>450 msec in the initial ECG among our patients.

Pediatric population studies: In the study of Samuel et al., 36 participants were divided into 3 groups. The groups were as follows; those taking HCQ alone, those taking the HCQ-AZT combination, and those not taking either drug. A statistically significant QT prolongation was found in the group receiving HCQ alone.[18] Significant arrhythmia was noted in 6 patients (17%). Significant ECG findings (longest daily measured QTc and baseline ECG abnormalities) were not significantly associated with arrhythmias. Our study is similar in this aspect.

In a single-center retrospective study by Tuncer et al., HCQ was used with or without AZT.[19] A total of 21 patients were included in the study. They reported that children in this patient group consisted of children who were not severely affected by COVID-19 infection. In this patient population, a serious arrhythmia did not develop as in our population. Our study also introduced additional parameters to the literature to assess the potential for arrhythmia.

In the review study of Parthasarathy et al. in the pediatric population, they reported that the literature on HCQ and QTc prolongation was variable. [20] They reported that QTc prolongation generally occurred on the 1st-4th day of drug use in studies.

In another study involving pediatric cases, data from 20 centers were evaluated. Treatment containing HCQ was started in 78 patients. ECG abnormality was not detected in any of these patients.[8] 59 patients used combination therapy containing HCQ and AZT. No significant arrhythmia developed in this group either. There was no serious illness in this population. This study supports our study in terms of study population and findings.

Conclusion

In general, there is a lack of information about the cardiac rhythm effects of therapeutic HCQ/AZT use in pediatric populations. We think that it will fill the knowledge gap in the literature on this subject. In cases of possible viral epidemics, upper respiratory tract pathogens show pathogenic characteristics with similar mechanisms. In such a case, reuse of these drugs in large patient populations may come to the fore due to their generally accepted antiviral activities. The effects of these drugs on myocardial action potential should be kept in mind. The drugs themselves are unlikely to prolong the QT and predispose to malignant ventricular arrhythmias, although they do exist.

Limitations of this article

The study was retrospective and carried out in a single center. Children who applied to the center and required hospitalization are few in number. These drugs were started in the early stages of the pandemic with the possibility of being effective in the treatment of the disease. In the treatment of COVID-19 infection, HCQ and AZT treatment were suspended in the next period.

The patient group consisted of the pediatric population. In this respect, data were collected in a limited area in a relatively less patient population (patient group that did not require intensive care follow-up). Considering the effects that can be seen in the use of these drugs other than intensive care; patients in this group will represent a larger number of people across the population. We hope that it will shed light on the future if it is used in indications arising from various requirements in the future.

Ethics Committee Approval

Ethics committee approval was obtained with the decision of the Ethics Committee for Non-Interventional Procedures of Adıyaman University, dated and numbered 2020: 8/11. The study was conducted under the principles of the Declaration of Helsinki.

Informed Consent

Data concerning the study were collected with the permission of the Adıyaman Provincial Health Directorate.

Authors Contrubituons

All of the authors contributed at every stage of the study

Conflict of Interests

There is no conflict of interest to declare.

Financial Disclosure

No person/organization is supporting this study financially.

Statements

These research results have yet to be presented anywhere previously. Data related to the study is available on request.

Peer-review

Externally peer-reviewed.

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