The Relationship Between QT Prolongation and Short Term Prognosis in Patients with Subarachnoid Hemorrhage Due to Aneursym Rupture

Anevrizma Kanamasına Bağlı Subaraknoid Kanamalarda QT Uzaması ile Prognoz İlişkisi

H.Önder OKAY, MD,[a]
Mehmet SEÇER, MD,[a]
Gürkan KUTUCULAROĞLU, MD,[b]
Ali DALGIÇ, MD,[a]
Ergün DAĞLIOĞLU, MD,[a]
Çağatay ÖZDÖL, MD,[a]
Osman Arıkan NACAR, MD,[a]
Rıfat AKDAĞ, MD,[a]
Fikret ERGÜNGÖR, MD[a]

[a]Neurosurgery Clinics,
[b]Cardiology Clinics,
Ankara Numune Education and Research Hospital, Ankara

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Yazışma Adresi/*Correspondence:*
Çağatay ÖZDÖL, MD
Ankara Numune Education and Research Hospital,
Neurosurgery Clinics, Ankara,
TÜRKİYE/TURKEY
cagatayozdol@yahoo.com

ABSTRACT Objective: Electrocardiographic (ECG) abnormalities and rhythm disorders are frequently observed in the acute phase of spontaneous subarachnoid hemorrhage (SAH). The pathophysiology of these abnormalities is considered to be related with the imbalance in autonomic cardiovascular control. There is no study yet showing the prognostic relevance of corrected QT interval (QTc) prolongation following subarachnoid hemorrhage in the Turkish population. **Material and Methods:** This retrospective study consisted of 33 SAH patients (7 male and 26 female) who were operated for aneurysm rupture in the Department of Neurosurgery between 2003 and 2005. Early ECG alterations of patients were evaluated by a cardiologist who was blinded for the prognosis of patients. We examined the relationship between prognosis and ECG findings. **Results:** Of the 33 SAH patients, those who died during hospitalization constituted the mortal group (n= 9), and the remaining patients the as survived group (n= 24). Baseline characteristics of the 2 groups were similar, however mean QTc values of mortal patients were significantly higher than in patients that survived (p= 0.034). In correlation analysis, we found that QTc interval was significantly correlated with Glasgow outcome scale (r= -0.39, p= 0.024). **Conclusion:** ECG should be evaluated in terms of QTc prolongation in SAH patients as a clinical prognostic finding.

Key Words: Subarachnoid hemorrhage; mortality; electrocardiography

ÖZET Amaç: Spontan subaraknoid kanama (SAK)'nın erken döneminde elektrokardiyografik (EKG) anormallikler ve ritim bozuklukları sık görülmektedir. Bu bozuklukların patofizyolojisinde kardiyovasküler sistemin otonomik kontrolünde dengesizliklerin rol oynadığı düşünülmektedir. Şimdiye kadar Türk popülasyonunda subaraknoid kanamayı takiben düzeltilmiş QT (QTc uzaması) intervalinin prognostik etkisini gösteren çalışma yoktur. **Gereç ve Yöntemler:** Bu retrospektif çalışma, 2003-2005 yılları arasında beyin cerrahisi kliniğinde anevrizma rüptürü nedeniyle opere edilen 33 SAK hastasını kapsamaktadır (7 erkek, 26 kadın). Hastaların erken EKG değişiklikleri, hastaların prognostik bilgisinden haberi olmayan bir kardiyolog tarafından değerlendirilmiştir. Biz bu çalışmada EKG bulguları ile prongoz arasındaki ilişkiyi inceledik. **Bulgular:** Toplam 33 hastadan hastane içi dönemde ölenler mortal grubu oluşturuken (n= 9), diğer hastalar sağkalan grubu oluşturmuştur (n= 24). Bu iki grubun bazal özellikleri benzemekle beraber, ölen hastaların ortalama QTc değerleri sağkalan hastalardan anlamlı oranda daha uzun idi (p= 0.034). Korelasyon analizinde, QTc intervali ile Glasgow sonlanım skalası arasında anlamlı bir korelasyon izlendi (r= -0.39, p= 0.024). **Sonuç:** Klinik olarak prognostik bilgi verebileceğinden, SAK hastalarında EKG, QTc uzaması yönünden değerlendirilmelidir.

Anahtar Kelimeler: Subaraknoid hemoraji; mortalite; elektrokardiyografi

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The most commoncause of SAH is aneurysm rupture in cerebral blood vessels.[1] The annual incidence of SAH is reported to be 7.5 to 12.9 per 100.000. It accounts for 22-25% of cerebrovascular deaths.[2] SAH

cause systemic complications including cardiopulmonary dysfunction, ECG abnormalities and pulmonary edema; however the pathophysiology of these complications is controversial.[3]

ECG changes of repolarization, including negative T wave, QT prolongation, ST elevation or depression following SAH were reported.[4-7] Repolarization changes are more common in hemispheric lesions compared to brain stem lesions.[6] Although there are some reports on the relationship between ECG changes and the mortality of patients with SAH, the prognostic value of these changes are still controversial.[8] We aimed to analyze the relationship between QT prolongation and short-term prognosis of patients who were operated for SAH due to aneurysm rupture.

MATERIAL AND METHODS

Thirty-seven consecutive patients who were operated for SAH due to aneurysm rupture in our clinic between 2003 and 2005 consisted the study population. The patients were diagnosed with neurological examination, lumbar puncture, cranial computerized tomography (CT) and cerebral angiography. Four cases were excluded from the study due to previous history of coronary artery disease, diabetes mellitus, neurological disease other than SAH, severe renal disease, previous history of a drug responsible for QT prolongation or marked electrolyte disturbance

Standard 12 lead ECGs of 33 patients obtained within the first 4 hours of their admission for SAH were evaluated by a cardiologist who was blinded for the names and prognosis of the patients. QT interval was measured manually from the beginning of the QRS complex to the end of the T wave where it connected to the isoelectric level and the longest QT interval in any of 12 leads was recoded. The connection of T and U waves was considered the end of the QT interval in the existence of U wave. When the connection of T and U waves was not clear, the connection of the U wave with the isoelectric level was considered the end of the QT interval. The longest QT interval was corrected for the heart rate in accordance with the Bazett Formula: QTc = QT/ (√R-R). Long QTc intervals of >450 msn for men and >460 msn for women were considered abnormal.[9]

Statistical Analysis

Analysis were performed using SPSS software package (version 13.0 for Windows, SPSS Inc., Chicago, Illinois). Data were expressed as numbers and percentages for discrete variables, means ± SD for continuous variables and median and interquartile range for other continuous variables. The chi-square analysis or the two-tailed Fischer's exact test, where appropriate, was used to assess the significance of differences between dichomatous variables. Continuous variables were compared by Student's *t* test, Mann-Whitney U test or Kruskal-Wallis analysis of variance test. Correlation analysis was carried out using Spearman's rank correlation test. Results with a p value < 0.05 were considered significant.

RESULTS

Of the patients included in the study, 7 (20.58%) were male, and 26 (79.42%) were female. Mean age of the group was 54.5 (30-72) years. The Glasgow outcome scale (GOS) is among the most common used outcome scales in neurosurgery and the patients were graded between 1 and 5, where 1 reflects mortality and 5 reflects complete recovery.[10] The patients were divided into 2 groups as mortal patients (GOS 1) and non-mortal ones (GOS 2, 3, 4, 5). The characteristics of these groups were presented in Table 1.

As shown in Figure 1 the mean QTc values of mortal patients were significantly higher than in patients that survived (492 ± 61 msec and 439 ± 36 msec, respectively). In addition, the percentage of long QT was significantly higher in mortal patients (Figure 2).

In correlation analysis, we found that QTc interval was significantly correlated with GOS (r= -0.39, p= 0.024) (Figure 3).

None of the patients experienced serious ventricular arrhythmia or arrhythmic death during the hospitalization period.

TABLE 1: Characteristics of 33 patients included in the study.

	Survived n= 24	Mortal n= 9	p
Age, years	53 ± 12	60 ± 10	0.11
Female sex	17 (71)	9 (100)	0.15
Hypertension	12 (50)	4 (44)	0.78
Diabetes mellitus	4 (17)	2 (22)	0.71
Systolic blood pressure, mmHg	152 ± 38	141 ± 28	0.44
Diastolic blood pressure, mmHg	85 ± 20	78 ± 14	0.30
Pulse rate (/min)	84 ± 13	81 ± 10	0.83
Serum creatinine, mg/dL	1.0 ± 0.2	0.98 ± 0.1	0.25
Potassium, meq/L	4.5 ± 0.7	4.2 ± 0.6	0.39
Calcium, mg/dl	9.5 ± 0.6	9.6 ± 0.8	0.59
WFNS	1.8 ± 1.1	2.3 ± 1.3	0.31
Fisher	2.8 ± 1.1	2.7 ± 0.7	0.80
Hunt	1.7 ± 1.0	2.2 ± 1.1	0.24

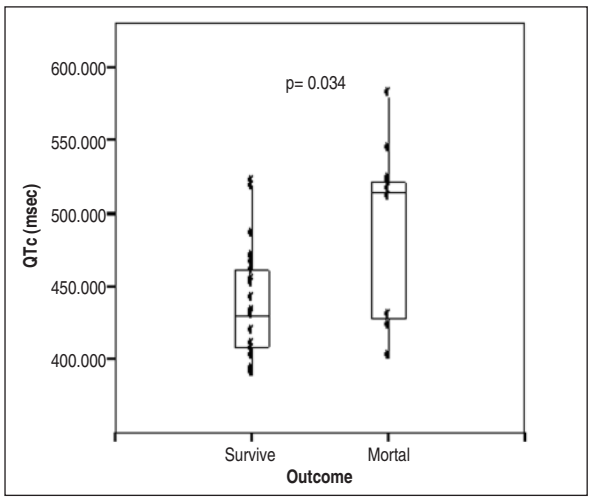

FIGURE 1: Median QTc values according to in-hospital survival outcome. Boxes cover the interquartile range (25th-75th percentile) where the line bisecting the box depicts the median. The whiskers extend to the 5th and 95th percentiles and circles depict individual values.

DISCUSSION

Cardiac effects of intracranial hemorrhage, rhythm and blood pressure changes were first reported in 1903 by Cushing.[11] Byer et al explained the ECG changes of SAH patients in 1947.[11,12] Several studies showed the relationship between prognosis of SAH patients and ECG abnormalities.[2-8,13-17] Maiuri et al suggested that ST segment depression, QT interval prolongation and pathological Q wave together showed poor prognosis.[14] Cruiskhank et al reported that pathological Q and ST elevations were both considered an indicator of poor diagnosis.[5] However, the incidence of Q wave or ST elevation is very low in SAH patients and their sensitivity values are low as well.[8] In our study mortal and non-mortal groups were compared based on QTc interval prolongation and mortal cases showed longer QT intervals (p= 0.034).

Brain stem possesses a cardiovascular regulatory system influencing both sympathetic and parasympathetic pathways and cardiac functions. Suprabulbar lesions such as intracranial tumors, cerebral trauma, encephalitis, intracerebral hemorrhage, cerebral infarct, and stroke including

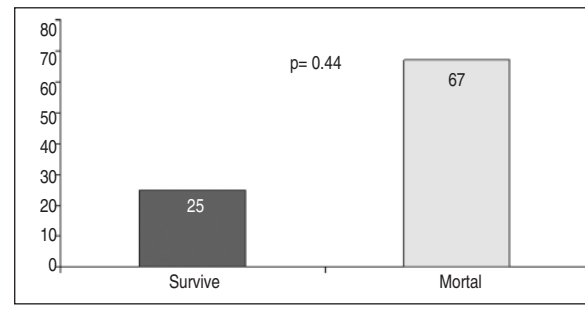

FIGURE 2: Percentage of patients with long QT interval according to survival outcome.

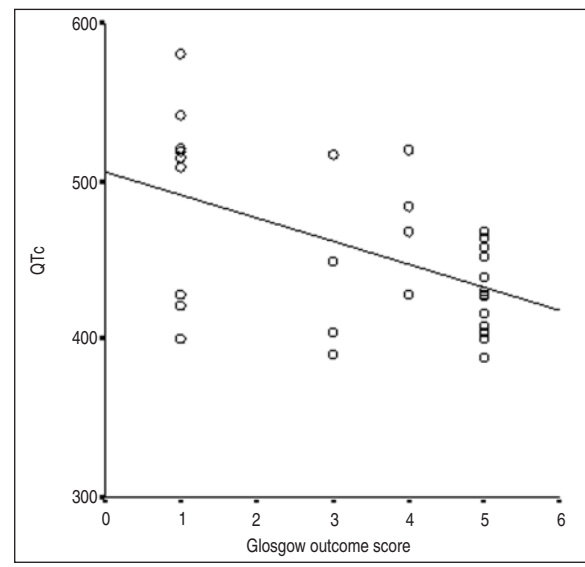

FIGURE 3: Scatter plots showing the correlation between QTc interval and GOS.

SAH cause changes in heart rate and ECG. However, these cardiac changes may be physiological and the underlying mechanism causing these changes is not clear. Supratentorial structures are also known to be associated with cardiovascular regulation.[6] Possible mechanisms may be presumed to explain the underlying mechanism of ECG abnormalities, such as electrolyte imbalance, the effect of aneurysm rupture on hypothalamic functions and myocardial injury related to intensive catecholamine secretion.[16] Some researches supported the data that hypokalemia and female gender were independent risk factors for severe QTc prolongation in patients with SAH.[13] The patients with electrolyte abnormalities were excluded from our study so that our study data would not support the mechanism of hypokalemia. On the other hand, all mortal cases were female and QTc intervals of women were more prolonged than the intervals of others in our study. In fact, prolonged QTc interval was observed in all mortal cases of our series.

Zaroff et al demonstrated myocardial dysfunction in dogs after SAH and the effects of catecholamine on heart by evaluating cardiac angiography and cardiac blood flow but this study was criticized for not evaluating intracranial pressure.[17] As animal studies suggested that antiadrenergic drugs inhibited cardiac injury after SAH, similar studies were conducted in humans.[15] Moreover, some studies suggested that increased intracranial pressure was of importance in cardiopulmonary dysfunction.[18] A number of autopsy series about SAH revealed petechial subendocardial hemorrhage and eosinophilic transverse bands in myocardial cell cytoplasm on histological examination.[19] Propranolol, an adrenergic blocker, when given alone or with phentolamin, was shown to decrease mortality and provide better prognosis in SAH patients compared to placebo.[20] Although the use of similar drugs in SAH is still controversial, some other studies reported that antihypertensive therapy affected the prognosis unfavorably in SAH patients.[21] Tung et al demonstrated a relationship between poor outcome and higher cardiac troponin I levels in SAH patients.[22] They pointed out the relation between the severity of SAH and the degree of myocardial necrosis. Interestingly they found that female sex was an independent predictor of high cardiac troponin I levels. They proposed further studies on this subject. Sakr et al studied the relationship between ECG changes and prognosis of SAH patients.[7] They found that ST depression strongly correlated with higher APACHE II scores and higher grades of Hunt-Hess classification, but they did not find any relationship between mortality and ST depression. However, changes that are more common like QT interval prolongation and U waves were not considered in this study.

The close relationship between cardiac complications and poor prognosis enforce the need for further studies.[2] Consequently, cardiac injury should be considered in SAH patients and it can be detected in routine preoperative ECG. In this study, the cases with prolonged QTc interval had a high mortality rate. Regardless of definitive explanation of the possible pathophysiological mechanisms underlying this condition, our study supports the data that ECG findings may have some value in predicting the prognosis of a SAH patient.

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