The Effect of Cilostazol on Electrocardiographic Parameters in Patients with Peripheral Artery Disease Initiating Cilostazol Treatment

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ABSTRACT

Introduction: One of the pharmacological treatment options for improving the symptoms of peripheral artery disease (PAD) and increasing the quality of life is cilostazol. Cilostazol is a pharmacological agent that shows vasodilator activity mainly by reducing cAMP degradation through specific cellular phosphodiesterase 3A enzyme inhibition. The effect of cilostazol on electrocardiographic parameters is not clear. In this study, we aimed to examine the effect of cilostazol on electrocardiographic parameters in PAD patients.

Patients and Methods: The study included a total of 32 patients diagnosed with intermittent claudication and peripheral artery disease (PAD), who were selected for medical treatment based on peripheral artery imaging. The subjects were started on 100 mg of cilostazol twice a day. The electrocardiographic measurements of the subjects before the cilostazol treatment and three months after the initiation of cilostazol were compared.

Results: After a period of three months, statistically significant prolongation was observed in the ventricular repolarization parameters QTd, QTc, and Tpe of the subjects compared to their premedication values (p= 0.01, for all).

Conclusion: It is known that patients with peripheral artery disease (PAD) are at an increased risk of major adverse cardiovascular events (MACE), including sudden cardiac death (SCD). In this context, close monitoring of electrocardiography markers for ventricular repolarization heterogeneity, such as QTd, QTc, and Tpe, is necessary when initiating cilostazol therapy in patients with peripheral artery disease (PAD). These markers may be closely associated with major adverse cardiovascular events (MACE), including sudden cardiac death (SCD), and therefore require careful monitoring in PAD patients receiving cilostazol treatment.

Key Words: Cilostazol; electrocardiographic parameters; peripheral artery disease

Periferik Arter Hastalığı Nedeniyle Silostazol Başlanan Hastalarda Silostazolün Elektrokardiyografik Parametreler Üzerine Etkisi

ÖZET

Giriş: Periferik arter hastalığı (PAH) semptomlarını düzeltmeye ve yaşam kalitesini artırmaya yönelik farmakolojik tedavi seçeneklerinden biri de silostazoldür. Silostazol, esas olarak spesifik hücresel fosfodiesteraz 3A enzim inhibisyonu yoluyla cAMP yıkımını azaltarak vazodilatör aktivite gösteren farmakolojik bir ajandır. Silostazolün elektrokardiyografik parametreler üzerindeki etkisi net olarak bilinmemektedir. Bu çalışmada PAH hastalarında silostazolün elektrokardiyografik parametreler üzerine etkisini incelemeyi amaçladık.

Hastalar ve Yöntem: Çalışmaya periferik arter görüntülemesi sonucunda intermittan kladikasyo tanısı konulan ve medikal tedaviye karar verilen 32 PAH hastası dahil edildi. Deneklere günde iki kez 100 mg silostazol başlandı. Olguların silostazol tedavisi öncesi ve silostazol başlandıktan üç ay sonraki elektrokardiyografik ölçümleri karşılaştırıldı.

Bulgular: Olguların elektrokardiyografik parametrelerinde üç ay sonra ventriküler repolarizasyon parametrelerinden QTd, QTc ve Tpe'de premedikasyon değerlerine göre istatistiksel olarak anlamlı uzama gözlendi (p= 0.01, tümü için).

Sonuç: PAH hastalarında ani kardiyak ölüm (AKÖ) gibi majör kardiyovasküler olayların (MACE) arttığı bilinmektedir. Bu bağlamda silostazol tedavisi başlanan PAH hastalarında MACE ile yakından ilişkili olabilecek QTd, QTc ve Tpe gibi ventriküler repolarizasyon heterojenite elektrokardiyografi belirteçlerinin yakın takibi yapılmalıdır.

Anahtar Kelimeler: Silostazol; elektrokardiyografik parametreler; periferik arter hastalığı

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INTRODUCTION

Peripheral artery disease (PAD) has emerged as a significant cause of both mortality and morbidity. This increase in prevalence can be attributed to the growing population affected by atherosclerotic risk factors such as aging, diabetes, smoking, and sedentary lifestyles[1]. Approximately 40% of patients with peripheral artery disease have intermittent claudication[2]. The initial treatment of intermittent claudication includes drug therapy, lifestyle changes, and exercise[3]. Cilostazol has seen a recent surge in its utilization as a pharmacological agent for the treatment of peripheral artery disease (PAD). Its use aims to alleviate symptoms and enhance the quality of life for individuals afflicted by this condition. Many clinical studies have shown that cilostazol significantly improves initial and long-term walking distances in patients with stable, moderate to severe intermittent claudication[4,5].

Cilostazol is a quinolone derivative, it reduces intracellular cAMP degradation by inhibiting cellular phosphodiesterase (especially phosphodiesterase-3)[6]. As a result, it contributes to vasodilation, inhibition of platelet activation and aggregation, improvement in serum lipids, and regression of atherosclerotic plaques[6,7]. There are conflicting reports in the literature on the cardiovascular effects of cilostazol. It has been suggested that cilostazol suppresses the transient outward potassium (Ito) flow and increases the inward calcium flow in patients with Brugada syndrome, thus protecting the action potential dome (phase 2), reducing the transmural dispersion of repolarization, and preventing ventricular fibrillation[8]. While PDE3 inhibitors are generally known to induce cardiac arrhythmias, particularly in patients with heart failure, it has been proposed that cilostazol may exhibit a reduced risk of this side effect due to its inhibition of adenosine uptake[8]. Contrary to these observations, cilostazol has been associated with an increased incidence of ventricular tachycardia and mortality. However, it has also been noted to have beneficial effects on reducing cardiac remodeling and improving cardiac function in cases of congestive heart failure resulting from myocardial infarction[9]. Although it has been suggested that an excessive cAMP level may contribute to increased ventricular arrhythmias and mortality in cilostazol-treated animals, the determinants of this effect have not been fully elucidated[9].

Considering the possible cardiac side effects of peripheral artery disease and cilostazol, electrocardiographic changes due to cilostazol may shed more light on these interactions. For this purpose, we aimed to examine the effect of cilostazol on predictive parameters of ventricular arrhythmia. To our knowledge, this is the first study to examine the long-term effect of cilostazol on ventricular repolarization indices in patients with peripheral artery disease.

PATIENTS and METHODS

Trial Design and Study Population

In this study, the medical records of 400 PAD patients who applied to our center for treatment between January 2014 and January 2017 were reviewed retrospectively. Only 32 of these patients met all study criteria and were included in the study (Figure 1). Of the 32 patients, four (12.5%) were female and 28 (87.5%) were male. ECG parameters were compared before and three months after initiating cilostazol treatment

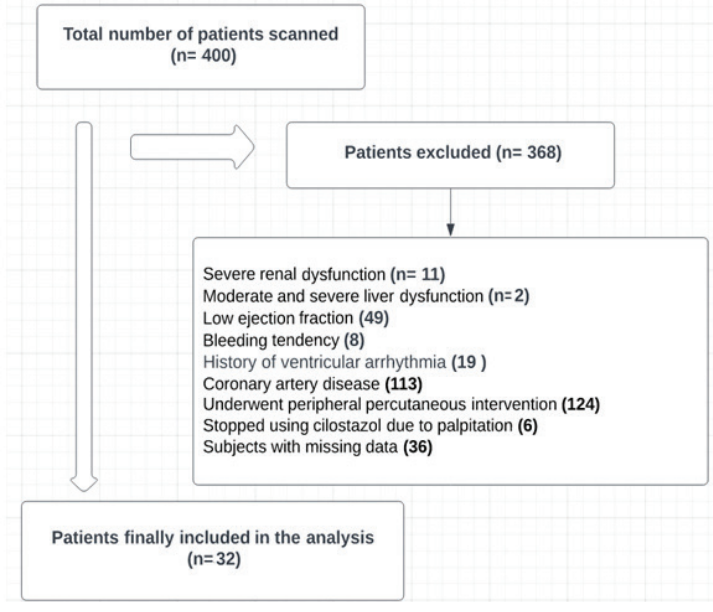

Figure 1. Flow chart of the subjects included in the study.

in patients with intermittent claudication. The study excluded individuals who had allergies to the active substance or any of the excipients, severe renal dysfunction (creatinine clearance ≤25 mL/min), moderate to severe liver dysfunction, low ejection fraction (<50%), bleeding tendencies (such as active ulcers or recent hemorrhagic stroke within the last six months), progressive diabetic retinopathy, uncontrolled hypertension, patients using anti-arrhythmic drugs that may impact ventricular repolarization markers, those with a history of ventricular tachycardia, patients with frequent multifocal ventricular ectopic beats and significant QT prolongation in ECG, individuals with a history of coronary artery disease, patients who underwent peripheral percutaneous intervention, patients who initially started cilostazol for PAD but discontinued due to palpitations, and subjects with missing data. Patients who were diagnosed with peripheral artery disease and started cilostazol in accordance with the guidelines by computed tomography or conventional angiography were included in the study[1]. In addition to cilostazol therapy, all patients were advised to undergo supervised exercise training and abstain from smoking in order to improve symptoms, enhance the quality of life, and reduce the risk of cardiovascular and limb events. Furthermore, lipid-lowering therapy and antiplatelet therapy were initiated as part of the treatment plan.

The study was approved by the ethics committee of Kartal Koşuyolu High Specialization Training and Research Hospital and was performed in accordance with the Declaration of Helsinki guidelines. Since the study was retrospectively designed, it was not considered necessary to obtain informed consent in accordance with the ethics committee rules.

Analysis of Electrocardiographic Parameters

ECGs taken before premedication and ECGs at least three months after starting cilostazol treatment were used in the evaluation. Measurements were made with a 3x magnifying lens and a precision ruler (± 0.02 mm accuracy) from TorQ company with a 150 mm digital caliper and an LCD display for easy reading. In the study, 12-lead recorded ECG data taken at 25 mm/s speed and 10 mm/mV amplitude were used as standard (Figure 2). QT interval measurement was made over leads V5-V6 and DII. The distance from the beginning of the QRS complex to the end of the T wave was measured. In the presence of a U wave, if the U wave is adjacent to the T wave, the end of the U wave was accepted as the QT interval. In the presence of an independent U wave, the QT interval was measured as the end of the T wave. The corrected QT (QTc) value of patients with a heart rate of 60-100 bpm was determined by using Bazett's formula; The QTc value of patients with a heart rate below 60 and above 100 was calculated using the Frederica formula[10]. For QT dispersion (QTd), the difference between the longest Qt distance and the shortest QT distance was taken. Pericordial leads were used for QTd measurements. For Tpe measurement, a vertical line was drawn from the peak of the T wave to the isoelectric line. The distance between the point where this vertical line intersects the isoelectric line and the end of the T wave was calculated as the Tpe time. Until now, there is no standardization regarding the derivations from which Tpe measurement will be made. Pericordial leads have been used frequently in studies conducted so far. In this study, we used the pericordial leads V1, V5, and V6 for Tpe measurements. Measurements were made by at least two experienced cardiologists. The intraobserver and interobserver variability for the analyses was less than 5%.

Statistical Analysis

The data analysis was conducted using SPSS 20 (Statistical Package for Social Sciences, SPSS Inc., Chicago, IL, USA), which is a software package developed by IBM. Descriptive

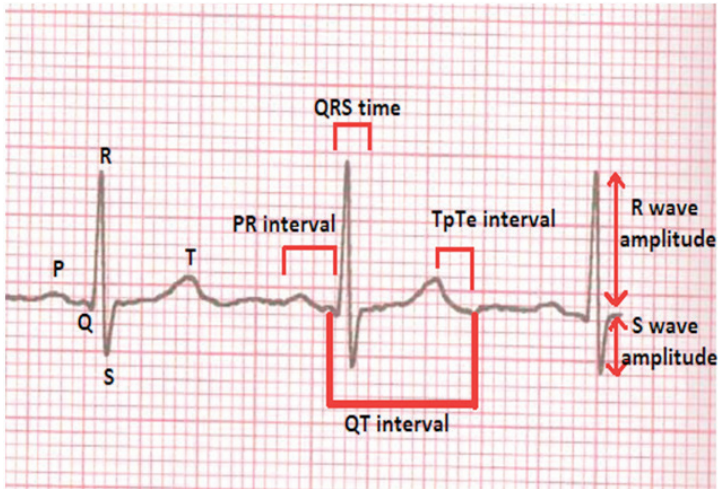

Figure 2. Display of electrocardiographic parameters on the ECG output.

statistical methods, such as percentages, frequencies, standard deviations, and means, were employed to analyze the study data. For the comparison of parameters between groups, an independent samples t-test was utilized. The results were evaluated at a 95% confidence interval with a significance level set at $p< 0.05$.

RESULTS

A total of 32 subjects (4 female and 28 male) were included in the study. The baseline demographic and clinical characteristics of the subjects are shown in Table 1. Table 2 displays the comparison of electrocardiographic values before premedication and electrocardiographic parameters at least three months after initiating cilostazol treatment for the subjects included in the study. No statistically significant change was observed in premedication and post-medication heart rate, PR interval, QRS time, and QT interval values ($p> 0.05$, for all). Post-medication QTc interval, QTd, and Tpe time values were observed to increase statistically significantly compared to pre-medication values (430.93 ± 33.25 vs. 414.34 ± 32.46, p= 0.01; 31.87 ± 17.11 vs. 30.59 ± 19.46, p= 0.01; 86.81 ± 23.42 vs. 79.09 ± 18.69, p= 0.001; respectively).

Table 1. Basic demographic and clinical characteristics of subjects

Age, years	60.51 ± 7.30
Male gender, n (%)	28 (87.5)
Body mass index, kg/m^2	24.4 ± 4.1
Smoking, n (%)	25 (78.1)
Chronic kidney disease, n (%)	5 (10.4)
Hypertension, n (%)	18 (56.3)
Diabetes mellitus, n (%)	14 (43.8)
Hyperlipidemia, n (%)	18 (56.3)

Values are expressed as % and mean ± SD.

DISCUSSION

In this study, we aimed to evaluate the possible effect of cilostazol on electrocardiographic parameters in patients with intermittent claudication due to peripheral artery disease. As a result of our study, we observed a statistically significant increase in the QTc interval, QTd, and Tpe times, which are among the ventricular repolarization indices. Therefore, we suggest close monitoring of patients with PAD who are started on cilostazol medication, as increased ventricular repolarization indices may be associated with outcomes such as malignant ventricular arrhythmias and sudden cardiac death.

Peripheral artery disease is encountered with increasing frequency all over the world due to prolonged life expectancy and exposure to increased risk factors such as sedentary life, diabetes, and smoking, and has become one of the important causes of mortality and morbidity[11,12]. PAD treatment includes secondary prevention, conservative treatment, and interventional treatments[3]. Secondary prevention is generally of great importance due to improving the course of the disease and the high risk of future cardiovascular events[13]. Two strategies are currently used to increase walking distance: exercise therapy and medical therapy[14,15]. Pentoxifylline, buflomedil, propionyl L-carnitine, and cilostazol are some of the treatment options to increase walking distance[16]. Among these pharmacological agents, only cilostazol has demonstrated proven efficacy in various randomized clinical trials[17,18].

Cilostazol is a quinolone derivative that inhibits cellular phosphodiesterase (especially phosphodiesterase 3, PDE3). Many organs, including the heart, contain members of all known PDE isoenzyme families. Since this group of drugs inhibits intracellular phosphodiesterase group enzymes, they increase intracellular cyclic adenosine monophosphate (cAMP) levels. In addition, cilostazol increases the current of L-type calcium channels. With these properties, it has dromotropic

Table 2. Comparison of pre-medication and post-medication electrocardiographic parameters of patients who started cilostazol

ECG parameters	Pre-medication measurements (n= 32)	Post-medication measurements (n= 32)	p
Heart Rate, bpm	68.7 ± 13.6	74.6 ± 11.5	0.067
PR interval, (ms)	156.5 ± 17.1	142.4 ± 20.6	0.418
QRS time, (ms)	87.6 ± 10.3	86.9 ± 8.8	0.601
QT interval, (ms)	389.5 ± 22.7	391.2 ± 31.4	0.345
QTc interval,(ms)	414.34 ± 32.46	430.93 ± 33.25	**0.01**
QTd, (ms)	30.59 ± 19.46	31.87 ± 17.11	**0.01**
Tpe time, (ms)	79.09 ± 18.69	86.81 ± 23.42	**0.01**

Values are expressed as mean ± SD.

and chronotropic effects, which create a predisposition to arrhythmias[19,20]. Various PDE3 inhibitors have also been reported to induce malignant ventricular arrhythmias and increase mortality in patients with congestive heart failure (CHF)[21,22]; however, there is insufficient evidence that cilostazol shows such adverse effects[23]. Although there are studies in the literature suggesting that cilostazol may be a pre-arrhythmogenic drug, there are also publications showing that it may have an anti-arrhythmogenic effect[8,9]. Gamssari et al. documented the development of ventricular tachycardia two days after initiation of cilostazol therapy in a patient with PAD without underlying heart disease[24]. Although cilostazol improved cardiac function in congestive heart failure in an experimental study, increased mortality associated with ventricular arrhythmias was demonstrated in cilostazol-treated control animals[25]. In an experimental study conducted by Barta et al., it was demonstrated that cilostazol might lead to an increase in ventricular arrhythmias and associated mortality[9]. In these experimental studies, it has been suggested that the pre-arrhythmogenic effect of cilostazol use is regulated by intracellular cyclic adenosine monophosphate (cAMP) levels, and this change may be a mechanism that may be involved in mediating electrocardiographic changes[9,26].

It is known to produce a potential proarrhythmic state through prolongation of the QTc interval, increased early post-depolarizations, or exposure of the heart to reentry circuits[27]. Ventricular repolarization times (QT interval) differ between superficial ECG leads. Studies have indicated that a significant difference in repolarization times, specifically QTd (QT dispersion), may elevate the risk of arrhythmias[28]. In experimental studies, the difference in action potential duration between middle myocardial M cells, epicardial and endocardial cells is reflected as transmural dispersion of repolarization (DoR), which is shown as Tpe on the superficial ECG. DoR is an important factor for reentering arrhythmias. Lubinski et al. reported that Tpe correlated with inducible ventricular tachycardia (VT)/ventricular fibrillation (VF)[29]. Watanabe et al. conducted a study demonstrating that electrophysiological studies in patients with prolonged times can induce ventricular tachycardia (VT). In addition, the same team suggested that prolonged Tpe causes spontaneous VT formation in patients[30]. Hence, Tpe has been proposed as a risk marker for ventricular arrhythmias. As a result, the QTc interval, QTd, and Tpe duration are considered electrocardiographic markers that reflect the heterogeneity of ventricular repolarization and are utilized in predicting arrhythmias. In our study, we observed a statistically significant prolongation of QTc interval, QTd, and Tpe durations in patients with peripheral arterial disease (PAD) who had been started on cilostazol treatment for intermittent claudication. While there is no consensus, these findings provide additional support to the hypothesis that cilostazol may have pro-arrhythmogenic effects. Although some earlier studies have suggested that the inhibition of adenosine uptake by cilostazol may counteract the pro-arrhythmic effect of cAMP, thereby mitigating its cardiac side effects[8,23], the results of our study, as well as some previous studies, do not support this hypothesis[9,24,31]. It is understood that various PDE3 inhibitors possess different arrhythmogenic potentials due to their positive inotropic effects, which result in increased intracellular Ca^2+ levels mediated by cAMP[32]. When comparing the arrhythmogenic effects of cilostazol and other PDE3 inhibitors in guinea pig hearts, cilostazol has been shown to have the least positive inotropic and L-type Ca^{2+} flow-increasing effect[33], suggesting that cilostazol is probably less arrhythmogenic than other PDE3s.

Our study had several limitations. Firstly, it was a single-center, retrospective study conducted with a small study population. Secondly, the lack of available data prevented the recording of serial ECG measurements for the subjects. Lastly, the long-term outcomes of the patients were not evaluated in our study. Addressing these limitations would enhance the value of our work.

CONCLUSION

Peripheral artery disease is known to be an independent risk factor for major adverse cardiovascular events such as sudden cardiac death[13]. This raises the concern that the pro-arrhythmogenic effect of cilostazol in PAD patients may have a synergistic effect on MACE. At conventional doses, the clinical benefits of using cilostazol may outweigh the risk of its pro-arrhythmogenic effects in most patients. However, given the fact that peripheral artery disease is often accompanied by a major pro-arrhythmogenic status such as ischemic heart disease, the increased risk of arrhythmias for patients with PAD treated with cilostazol should be kept in mind. Therefore, the use of cilostazol in PAD patients may require close electrocardiographic monitoring, especially if there is accompanying ischemic heart disease.

Ethics Committee Approval: The study was approved by the ethics committee of Kartal Koşuyolu Clinical Research Ethics Committee (Decision no: 28, Date: 19/06/2017) and was performed in accordance with the guidelines of the Declaration of Helsinki.

Informed Consent: This is retrospective study, we could not obtain written informed consent from the participants.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept/Design - BO, KT; Analysis/Interpretation – BO, KT, Kİ; Data Collection - BO, KT; Writing - BO, KT; Critical Revision - EA, MS, BO, KT; Final Approval- All of authors; Statistical Analysis – KT, Kİ; Overall Responsibility - BO.

Conflict of Interest: The authors have no conflicts of interest to declare.

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