

The Comparison of the Effects of the Cilostazol on the Stiffness Parameters in Different Arterial Systems in the Patients with Peripheral Arterial Disease

Periferik Arter Hastalığı Olan Hastalarda Silostazolün Farklı Arteriyel Sistemlerdeki Sertlik Parametreleri Üzerine Etkilerinin Karşılaştırılması

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Özet

Amaç: Noninvasiv yöntemler kullanılarak, stabil IK/PAH hastalarında silostazolünün arteriyel uyum, distensibilite, damar sertliğini ve diğer vasküler olaylara etkisini tespit etmek.

Gereç ve Yöntemler: Altı ay boyunca günde iki kez 100 mg silostazol ile tedavi edilen yirmi dokuz hasta (22 erkek, 7 kadın) çalışmaya dâhil edildi. Karotid, femoral ve brakiyal arter ultrason ölçümleri başlangıçta ve tedavi başladıktan sonra üçüncü ve altıncı ay sonrasında yapıldı. Arteriyel sertlik ölçümlerinin değerlendirilmesi noninvasiv yöntemlerle yapıldı. Arteriyel sertlik ölçümlerinin değerlendirilmesi önceden tanımlanmış yöntemle gerçekleştirildi.

Bulgular: Olguların yaş ortalaması 64 yıl idi. Karotid, femoral ve brakiyal arterde tedavi ile kesitsel uyum, kesitsel esneklik ve diyastolik duvar gerilme değerlerinin arttığı; pulsatilite indeksi, rezistif indeks, sistolik/diyastolik hız oranı, intima-media kalınlığı ve elastik modül değerlerinin azaldığı saptandı. Karotis, femoral ve brakiyal arterlerdeki değişimin benzer oranları vardı.

Sonuç: Periferik arter hastalığı olan hastalarda silostazol tedavisi uzun süreli izlemede kanama riskini artırmadan aterosklerozun ilerlemesini azaltır.

Anahtar kelimeler: Periferik arter hastalığı; İntima-media kalınlığı; Arteriyel sertlik; Silostazol; Kesitsel uyum; Kesitsel distensibilite; Diyastolik duvar stresi; Elastik modül

Abstract

Objective: Object of this study is to determine the effect of cilostazol on arterial compliance, distensibility and vascular stiffness in carotid, femoral and brachial arteries through non-invasive methods in patients with stable IC/PAD.

Material and Methods: Twenty-nine patients (22 male, 7 female) who had been treated with cilostazol 100 mg twice daily during six month were included in the study. Ultrasound measurements of carotid, femoral and brachial arteries were performed at baseline, at 3 and 6 months after starting of treatment and the evaluation of the arterial stiffness measurements were performed by the pre-defined method.

Results: The mean age of the participants was 64 years. Pulsatility index, resistive index, systolic/diastolic velocity ratio, intima-media thickness and elastic modulus values were decreased while cross-sectional compliance, cross-sectional distensibility and diastolic wall stress values were increased with treatment in carotid, femoral and brachial arteries. Carotid, femoral and brachial arteries have similar rates of change.

Conclusion: Cilostazol treatment reduced the progression of atherosclerosis without increasing the risk of bleeding in patients with peripheral arterial disease during a long-term follow-up.

Key words: Peripheral arterial disease; Intima-media thickness; Arterial stiffness; Cilostazol; Cross-sectional compliance; Cross-sectional distensibility; Diastolic wall stress; Elastic modulus

INTRODUCTION

Peripheral arterial disease (PAD) affects 20% of people over 70 years of age and 4% to 12% of the population aged 55 to 70 years (1-3). Approximately 40% of those affected with PAD commonly complain of intermittent claudication (IC) (2). Despite the relatively benign prognosis for the affected leg, the symptoms of IC are an indicator for the development of systemic atherosclerosis. Compared with age-matched controls, people with IC have a three to six fold increased chance of dying as a result of cardiovascular events (4).

The majority of patients with IC are treated with best medical management. Antiplatelet treatment is given to reduce the risk of cerebrovascular and coronary events. It is effective in the long-term

secondary prevention of vascular events in people at high risk of vascular disease, including those who have had ischemic stroke or acute myocardial infarction (MI) (5).

Many pharmacological agents have been advocated for treating IC. Cilostazol is a phosphodiesterase III inhibitor with pharmacological effects that include vasodilation, inhibition of platelet activation and aggregation, inhibition of thrombosis, increased blood flow to the limbs, improvement in serum lipids with lowering of triglycerides, elevation of high density lipoprotein cholesterol and inhibition of vascular smooth muscle cell growth. Cilostazol has been shown to be of benefit in improving pain-free walking distance in people with IC. There is no

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sufficient data on whether it results in a reduction of vascular events (3, 6-15).

Functional disorders of the arterial wall may develop much earlier than the appearance of the clinical signs of vascular disease and structural changes of the arterial wall (16). Numerous methods were developed in order to determine existence and prevalence of arteriosclerosis noninvasively. Intima-media thickness (IMT) and arterial stiffness measurements are among the most common methods (17, 18). The factor which causes mechanical stress in physiology of arterial structures is called pressure while the changes in the diameter due to pressure are called strain. The relationship between these two physiological conditions reflects arterial elasticity and stiffness. Quantitative counterparts of elasticity and stiffness are compliance and distensibility. Distensibility implies proportional change due to increase in pressure while compliance implies the absolute change in diameter due to increase in pressure (17).

Object of this study is to determine the effect of cilostazol on arterial compliance, distensibility and vascular stiffness in carotid, femoral and brachial arteries through non-invasive methods in patients with stable IC/PAD.

MATERIAL AND METHODS

Ethics

Ethical approval was obtained from the Ethics Committee of our institution

Study design

Twenty-nine patients with IC (22 male, 7 female), who had been clinically referred for Doppler US examination for peripheral artery were included in the study. The patients had received cilostazol (Pletal, Otsuka Pharmaceutical Co., Osaka, Japan) 100 mg twice daily treatment during six months.

Inclusion criteria: > 45 years; confirmed PAD; at least 6 month history of stable symptomatic IC secondary to PAD; and reproducible walking distances on screening treadmill.

Exclusion criteria: Limb-threatening chronic limb ischemia (ischemic rest pain, ulceration or gangrene); gross obesity; childbearing potential; inability to complete the treadmill walking test; hypertension; current malignancy; exercise limiting cardiac disease; MI within previous 6 months; concomitant use of antiplatelet, anticoagulant, hemorrhagic, vasoactive, or NSAIDs; lower extremity surgical or endovascular reconstruction or sympathectomy in previous 6 months; DVT within previous 3 months; severe concomitant disease; substance abuse; Buerger's disease; tendency to bleeding; or platelet count < 130,000/cm³ or hematocrit < 30%.

Age, weight, height, and waist and hip circumference measurements, and the other findings of the patients were recorded.

Ultrasound measurements and stiffness analysis

Ultrasound measurements were performed at baseline, at 3 and 6 months after starting of treatment.

All non-invasive measurements were made by the same investigator. The Doppler ultrasound examinations via SSA-660A ultrasound system (Xario) and PLT-704AT Probe (Toshiba Medical Systems Corporation, Tochigi, Japan). The probe was placed 2 cm proximal to bifurcation of the right carotid artery, 2 cm distal to the separation of the deep branch of the right femoral artery and right brachial artery at level of antecubital fossa, and the evaluation of the arterial stiffness measurements were performed by the pre-defined method (19).

Intima-media thickness and lumen diastolic (dD) and systolic (sD) diameters were measured at the common carotid, femoral and brachial artery. Lumen cross-sectional area was calculated as $\pi dD^2/4$ and wall cross-sectional area as $\pi(dD/2+IMT)^2-\pi(dD/2)^2$. Cross-sectional compliance (CSC) and distensibility (CSD) of the common carotid artery were calculated from diameter changes during systole and from simultaneously measured pulse pressure (ΔP) according to the following formulae: Cross-sectional compliance = $\pi[(sD^2-dD^2)]/4\Delta P$; Cross-sectional distensibility = $(sD^2-dD^2)/(dD^2.\Delta P)$ and Diastolic wall stress (DWS) was calculated as mean arterial pressure multiplied by $dD/2IMT$. Whereas compliance provides information on elasticity of the artery as a hollow structure, incremental elastic modulus (EM) provides information on the properties of the wall material independently from arterial geometry. This variable was calculated as $3/(1+lumen\ cross\ sectional\ area/wall\ cross\ sectional\ area)$ divided by cross-sectional distensibility.

Arterial blood pressure measurements of the subjects were performed by an automatic sphygmomanometer (Vitagnost 2015 OC, MARS, Taiwan).

Statistical analysis

Data are expressed as mean \pm SD for variables. The comparisons between before and after treatment were analyzed two-way repeated-measures analysis of variance (ANOVA) using SPSS for Windows v.15.0 (SPSS Inc., Michigan, IL, USA) software. A p value <0.05 was considered as the level of significance.

RESULTS

The mean age of the participants was 64 years (range, 46-80 years). The mean values of BMI (kg/m²) and WHR are 26.64 ± 4.75 (range, 20.55-34.84) and 0.90 ± 0.08 (range, 0.77-1.00) respectively.

The results, given in detail below, are shown in Table I.

Elastic modulus values were decreased while CSC, CSD and DWS values were increased with treatment in carotid, femoral and brachial arteries.

Carotid artery IMT values at baseline, 3rd month and 6th month after treatment, are 0.61 ± 0.23 , 0.41 ± 0.16 and 0.31 ± 0.12 , respectively. The percentages of alteration between samples, second versus first, third versus second and third versus first were 32.79% ($p<0.001$), 24.39% ($p<0.001$), 49.18% ($p<0.001$), respectively.

Carotid artery CSC values at baseline, 3rd month and 6th month after treatment, are 0.1870 ± 0.1509 ,

Table I. Descriptive values of measurements of carotid, femoral and brachial arteries.

Artery		Mean±SD			p value 1 vs 2	p value 2 vs 3	p value 1 vs 3	% value 1 vs 2	% value 2 vs 3	% value 1 vs 3
		1st sample (Baseline)	2nd sample (3 rd month)	3th sample (6 th month)						
Carotid	IMT	0.61±0.23	0.41±0.16	0.31±0.12	0.001	0.001	0.001	32.79	24.39	49.18
	CSC	0.1870±0.1509	0.2487±0.1822	0.2959±0.2412	0.001	0.024	0.001	32.99	18.98	58.24
	CSD	0.0088±0.0093	0.0118±0.0126	0.0177±0.0169	0.001	0.001	0.001	34.09	50.00	101.14
	DWS	504.54±222.62	596.7±243.52	814.56±348.34	0.001	0.001	0.001	18.27	36.51	61.45
	EM	155.75±81.54	116.25±61.79	38.18±37.06	0.001	0.001	0.001	25.36	67.16	75.49
Femoral	IMT	0.50±0.16	0.40±0.11	0.19±0.12	0.001	0.001	0.001	20.00	52.50	62.00
	CSC	0.0550±0.0483	0.1105±0.0740	0.2423±0.1746	0.001	0.001	0.001	100.91	119.28	340.55
	CSD	0.0055±0.0064	0.0092±0.0107	0.0150±0.0131	0.001	0.001	0.001	67.27	63.04	172.73
	DWS	550.84±180.05	622.82±211.46	721.73±238.74	0.001	0.001	0.001	13.07	15.88	31.02
	EM	239.97±149.94	184.31±113.87	104.54±91.44	0.001	0.001	0.001	23.19	43.28	56.44
Brachial	IMT	0.33±0.11	0.25±0.10	0.22±0.09	0.001	0.001	0.001	24.24	12.00	33.33
	CSC	0.0535±0.0403	0.1015±0.0660	0.2019±0.1286	0.001	0.001	0.001	89.72	98.92	277.38
	CSD	0.0106±0.0085	0.0115±0.0084	0.0252±0.0222	0.002	0.001	0.001	8.49	119.13	137.74
	DWS	169.45±82.65	248.29±121.70	315.08±151.55	0.001	0.001	0.001	46.53	26.90	85.94
	EM	135.81±114.35	96.54±86.96	85.70±75.38	0.001	0.001	0.001	28.92	11.23	36.90

IMT: Intima-media thickness (mm); CSC: Cross-sectional compliance; CSD: Cross-sectional distensibility; DWS: Diastolic wall stress; EM: Elastic modulus; vs: versus.

0.2487±0.1822 and 0.2959±0.2412, respectively. The percentages of alteration between samples, second versus first, third versus second and third versus first were 32.99% (p<0.001), 18.98% (p<0.024), 58.24% (p<0.001), respectively.

Carotid artery CSD values at baseline, 3rd month and 6th month after treatment, are 0.0088±0.0093, 0.0118±0.0126 and 0.0177±0.0169, respectively. The percentages of alteration between samples, second versus first, third versus second and third versus first were 34.09% (p<0.001), 50.00% (p<0.001), 101.14% (p<0.001), respectively.

Carotid artery DWS values at baseline, 3rd month and 6th month after treatment, are 504.54±222.62, 596.7±243.52 and 814.56±348.34, respectively. The percentages of alteration between samples, second versus first, third versus second and third versus first were 18.27% (p<0.001), 36.51% (p<0.001), 61.45% (p<0.001), respectively.

Carotid artery EM values at baseline, 3rd month and 6th month after treatment, are 155.75±81.54, 116.25±61.79 and 38.18±37.06, respectively. The percentages of alteration between samples, second versus first, third versus second and third versus first were 25.36% (p<0.001), 67.16% (p<0.001), 75.49% (p<0.001), respectively.

Femoral artery IMT values at baseline, 3rd month and 6th month after treatment, are 0.50±0.16, 0.40±0.11 and 0.19±0.12, respectively. The percentages of alteration between samples, second versus first, third versus second and third versus first were 20.00% (p<0.001), 52.50% (p<0.001), 62.00% (p<0.001), respectively.

Femoral artery CSC values at baseline, 3rd month and 6th month after treatment, are 0.0550±0.0483, 0.1105±0.0740 and 0.2423±0.1746, respectively. The percentages of alteration between samples, second

versus first, third versus second and third versus first were 100.91% (p<0.001), 119.28% (p<0.001), 340.55% (p<0.001), respectively.

Femoral artery CSD values at baseline, 3rd month and 6th month after treatment, are 0.0055±0.0064, 0.0092±0.0107 and 0.0150±0.0131, respectively. The percentages of alteration between samples, second versus first, third versus second and third versus first were 67.27% (p<0.001), 63.04% (p<0.001), 172.73% (p<0.001), respectively.

Femoral artery DWS values at baseline, 3rd month and 6th month after treatment, are 550.84±180.05, 622.82±211.46 and 721.73±238.74, respectively. The percentages of alteration between samples, second versus first, third versus second and third versus first were 13.07% (p<0.001), 15.88% (p<0.001), 31.02% (p<0.001), respectively.

Femoral artery EM values at baseline, 3rd month and 6th month after treatment, are 239.97±149.94, 184.31±113.87 and 104.54±91.44, respectively. The percentages of alteration between samples, second versus first, third versus second and third versus first were 23.19% (p<0.001), 43.28% (p<0.001), 56.44% (p<0.001), respectively.

Brachial artery IMT values at baseline, 3rd month and 6th month after treatment, are 0.33±0.11, 0.25±0.10 and 0.22±0.09, respectively. The percentages of alteration between samples, second versus first, third versus second and third versus first were 24.24% (p<0.001), 12.00% (p<0.001), 33.33% (p<0.001), respectively.

Brachial artery CSC values at baseline, 3rd month and 6th month after treatment, are 0.0535±0.0403, 0.1015±0.0660 and 0.2019±0.1286, respectively. The percentages of alteration between samples, second versus first, third versus second and third versus first were 89.72% (p<0.001), 98.92% (p<0.001), 277.38%

($p < 0.001$), respectively.

Brachial artery CSD values at baseline, 3rd month and 6th month after treatment, are 0.0106 ± 0.0085 , 0.0115 ± 0.0084 and 0.0252 ± 0.0222 , respectively. The percentages of alteration between samples, second versus first, third versus second and third versus first were 8.49% ($p < 0.002$), 119.13% ($p < 0.001$), 137.74% ($p < 0.001$), respectively.

Brachial artery DWS values at baseline, 3rd month and 6th month after treatment, are 169.45 ± 82.65 , 248.29 ± 121.70 and 315.08 ± 151.55 , respectively. The percentages of alteration between samples, second versus first, third versus second and third versus first were 46.53% ($p < 0.001$), 26.90% ($p < 0.001$), 85.94% ($p < 0.001$), respectively.

Brachial artery EM values at baseline, 3rd month and 6th month after treatment, are 135.81 ± 114.35 , 96.54 ± 86.96 and 85.70 ± 75.38 , respectively. The percentages of alteration between samples, second versus first, third versus second and third versus first were 28.92% ($p < 0.001$), 11.23% ($p < 0.001$), 36.90% ($p < 0.001$), respectively.

Finally 1 versus 3, Carotid, Femoral and Brachial Artery: IMT, 49.18%, 62.00%, 33.33%; CSC, 58.24%, 340.55%, 277.38%; CSD, 101.14%, 172.73%, 137.74%; DWS, 61.45%, 31.02%, 85.94%; EM, 75.49%, 56.44%, 36.90% respectively.

DISCUSSION

Peripheral arterial disease affects 25% of people over 55 years of age. It is the manifestation of atherosclerosis in the lower extremities (2, 3). Patients with PAD commonly complain of IC, occurring in 40% of patients (2). Intermittent claudication is characterized by pain in the legs or buttocks that occurs with exercise and subsides with rest. Despite the relatively benign prognosis, the symptoms of IC are an indicator for systemic atherosclerosis. Compared with age-matched controls, people with IC have a three to six fold increase in cardiovascular mortality (4). The majority of patients with IC are treated with best medical management (5).

Various therapies such as statins, angiotensin-converting enzyme inhibitors and peroxisome proliferator-activated receptor- α activators have been shown to reduce cardiovascular events and to slow the progression of atherosclerosis (20).

Antiplatelet therapy is effective in long term secondary prevention of vascular events in patients at high risk of vascular disease, including those who have had ischemic stroke or acute MI. There is a benefit of antiplatelet treatment in patients with PAD in the reduction of vascular events (3, 13, 14).

Cilostazol is a phosphodiesterase III inhibitor with pharmacological effects that include vasodilation, inhibition of platelet activation and aggregation, inhibition of thrombosis, increased blood flow to the limbs, improvement in serum lipids with lowering of triglycerides and elevation of high density lipoprotein cholesterol, and inhibition of vascular smooth muscle cell growth (12).

The results of seven randomised double blind controlled studies (over 1500 patients) demonstrate

that cilostazol significantly improves the absolute and initial claudication distances in patients with stable, moderate to severe intermittent claudication. All trials included patients receiving 100 mg cilostazol twice daily or placebo. The benefits in improved walking distances were observed within a few weeks of starting the treatment and continued for the duration of these short studies (12 to 24 weeks) (1, 6-11).

Sonographic investigation of carotid, femoral and brachial arteries is quite important for noninvasive assessment of arteriosclerosis. Arterial stiffness is a term which implies stiffness on the vessel walls while arterials lose their elasticity and it is a component of arteriosclerosis. Numerous parameters were shown as the marker of arterial stiffness and these parameters are known to have no superiority over one another. Functional changes on vessel walls at early arteriosclerosis phase which generally occur before having a clinical symptom was mostly investigated in aorta, carotid, brachial and femoral arteries. Furthermore, IMT measurement in arteries is demonstrated to be a noninvasive and reliable marker in order to show existence and prevalence of arteriosclerosis (16, 21-23).

It is less clear whether cilostazol treatment can modify arterial IMT and arterial stiffness in patients with PAD during the relatively long-term follow-up period. In this study, we investigated the effects of a 200-mg dose of cilostazol administered on arterial IMT and stiffness progression in patients with PAD in 6-month follow-up.

There is a strong relationship between coronary artery disease and IMT of the main carotid artery, and between local atherosclerosis and IMT of the femoral artery. Increases in arterial IMT are associated with increased risk of future cerebrovascular and cardiovascular events (24, 25). Imaging techniques that used to visualize changes in arterial IMT play important roles in assessing disease development and response to medical therapy. With the use of non-invasive imaging techniques, it is possible to easily monitor the effects of medical therapy on the progression of arterial IMT. Therefore, the IMT measurement of the distant wall by high-resolution ultrasonography has been proven a beneficial clinical index in the early recognition of extremity and general atherosclerosis (19, 20, 26).

It has been show recently, cilostazol treatment reduced the progression of carotid IMT (20).

In our study, it is showed that cilostazol treatment reduced the carotid, femoral and brachial IMT (Table I).

Arterial distensibility is a measurement of expansion and contraction abilities of the arteries caused by cardiac pulsation and relaxation. Arterial flexibility was used as a new risk factor for cardiovascular disease in the design of the population-based cohort or cross-sectional studies, including the Atherosclerosis Risk in Communities (ARIC), the Second Manifestations of Arterial Diseases (SMART), the Rotterdam, the Baltimore Longitudinal Study of Aging (BLSA), and the Multi-Ethnic Study of Atherosclerosis (MESA) (16, 24, 27-29).

Indices of arterial stiffness, including pulse

wave velocity have been found higher among those with angiographic arterial disease as compared to individuals who do not have angiographic arterial disease, and some studies have demonstrated a positive correlation between arterial stiffness and the severity of arterial disease (30).

Cilostazol induced relaxation of the phenylephrine-precontracted thoracic aorta in a concentration dependent manner (31).

In our study, we showed that cilostazol treatment reduced the carotid, femoral and brachial stiffness and EM and increased of CSC, CSD and DWS parameters (Table I)

In IMT, CSC and CSD values the femoral system had been given a better percentage changing than the others. The IMT answer had been come true the least amount in brachial system. This position shows that the brachial artery IMT value has already been less at first than the others and because of the measurement scales parameters and the changing amount less and it has caused so on .Distal arterial systems are better than femoral systems and in stiffness parameters it had been taken better conclusions. It causes that in vascular position different in answers. Consequently, when it was looked at distal tonus in high vascular position cilostazol's effects are clearer than.

Cilostazol was well tolerated with an acceptable side effect profile. The most common side effects reported were headaches, nausea, diarrhea, pain, infection, upper respiratory symptoms and peripheral edema (15, 32).

In our study, neither non-tolerated nor non-acceptable side effects were seen in individuals. Some mild intensity symptoms are resolved with symptomatic treatment without requiring cessation of therapy.

Study limitations

Our study had a few limitations. Because we only included patients with PAD, our findings should not be extrapolated to the general population. This study included a relatively small number of participants. Therefore, multicenter studies with a larger number of participants are needed to confirm the effectiveness of cilostazol in reducing atherosclerotic progression.

Conclusions

Cilostazol treatment reduced the progression of atherosclerosis without increasing the risk of bleeding in patients during the 6-month follow-up period. A 200-mg dose of cilostazol can be safely and effectively used in preventing the atherosclerotic progression in patients with PAD during a long-term follow-up. Our data supposed that treatment with cilostazol reduced of cardiovascular events. Further studies in relation to the impact of cilostazol on quality of life, health economics and prevention of adverse cardiovascular events are also required.

Conflict of interest

There is no conflict of interest in connection with any commercial associations, and all authors have nothing to disclose.

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