Original article

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EFFICACY OF DRUG THERAPY IN PATIENTS WITH PERIPHERAL ARTERIAL DISEASE IN RELATION TO SMOKING

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Peripheral arterial disease is one of the manifestations of atherosclerosis that manifests itself primarily in the peripheral arteries of the lower extremities and the aorto-iliac segment. The largest number of patients, about 90%, have functional ischemia (Stage IIa and IIb according to Fontaine). For these patients, the therapy of choice is medication consisting of a combination of acetylsalicylic acid, cilostazol and pentoxifylline. Smoking is a very significant risk factor for the development of peripheral arterial disease and is also one of the most significant outcome modifiers. The study included 82 patients diagnosed with functional ischaemia of the lower extremities treated at the Clinic of Vascular Surgery of the Clinical Center in Niš, starting from January 2020 to December 31, 2020. Smoking was present in 76.82% of respondents. In the research conducted, 48.78% of respondents used pentoxifylline + acetylsalicylic acid, while 51.22% of respondents were treated with cilostazol + acetylsalicylic acid. Results showed the extension of the claudication distance after 6 months was significantly greater in the group of patients who used cilostazol + acetylsalicylic acid. In a subgroup of patients smoking > 20 cigars daily and with > 20 years of smoking there was a significant increase in claudication distance after 6 months in the cilostazol + acetylsalicylic acid group compared to pentoxifylline + acetylsalicylic acid group. In conclusion, the number of cigarettes/day and length of smoking experience have a significant effect on the applied therapeutic modality in patients with peripheral arterial disease. Cilostazol + acetylsalicylic acid therapy was more effective than pentoxifylline + acetylsalicylic acid.

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Key words: *peripheral arterial disease, medical treatment, smoking*

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Introduction

Peripheral arterial disease (PAD) is one of the manifestations of atherosclerosis that manifests itself primarily in the peripheral arteries of the lower extremities and the aorto-iliac segment and is a disorder in the normal functioning of the arterial system that leads to reduced blood flow in the extremities. The main clinical manifestation of functional ischemia of the lower extremities is intermittent claudication (1). Risk factors for PAD are hypertension, dyslipidemia, smoking, diabetes and genetic load (2). Considering that atherosclerosis is a systemic disease, 50%–75% of patients with peripheral arterial disease also suffer from coronary or cerebrovascular disease (3).

PAD therapy consists of risk factor control, drug therapy, endovascular and open surgical treatment.

The largest number of patients with PAD, about 90%, have functional ischemia (Stage IIa and IIb according to Fontaine). For these patients, the therapy of choice is medication consisting of a combination of ASA, cilostazol and pentoxifylline (4).

Pentoxifylline is a xanthine derivative whose main mechanism of action is haemolytic. Pentoxifylline enhances erythrocyte deformability, reduces blood viscosity and reduces platelet aggregation. Cilostazol is a phosphodiesterase III inhibitor and its main mechanisms of action in the treatment of PAD are relaxation of smooth muscle cells in blood vessels, stimulation of angiogenesis and antiaggregation. Numerous studies have shown the superiority of cilostazol over pentoxifylline, so it has largely supplanted pentoxifylline as the drug of first choice (5). However, cilostazol has numerous side effects such as dizziness, palpitations and nausea, which

leads to very poor long-term adherence to therapy. It has been shown that within 36 months, more than 60% of patients discontinue cilostazol therapy, leaving room for further use of pentoxifylline regardless of the superior effect of cilostazol (6).

Smoking is a very significant risk factor for the development of PAD and compared to non-smokers, active smokers have a five times higher risk of developing PAD. The effect of smoking on the cardiovascular system is very harmful considering that it damages the endothelium of the arteries and has an atherogenic effect. The mechanism by which smoking affects the development and progression of PAD is via the carbon monoxide and increased carboxy-hemoglobin levels (7). Also, smoking leads to a reduction in blood flow by activating vasospastic mechanisms and increasing blood viscosity. These disorders lead to the consequent activation of coagulation factors and a decrease in the elasticity of erythrocytes. Literature data have shown that there is a positive association between cigarette use and increased levels of triglycerides, cholesterol and low-density lipoprotein (LDL) with a decrease in the level of protective high-density lipoprotein (HDL) (8). A meta-analysis by Willigendael et al., which included 29 studies, showed that smoking in patients who underwent a revascularization procedure caused up to 3 times more frequent graft thrombosis compared to non-smokers. In this relationship between smoking and graft occlusion, the number of cigarettes consumed and the length of smoking experience had a significant relationship, while the type of prosthetic material was not significant. Cessation of smoking after performing the revascularization procedure allowed the patency of the grafts to be equivalent to that of non-smokers (9). Research that evaluates the effect of smoking on medical or conservative PAD therapy is practically non-existent.

This prospective study aims to determine the influence of smoking on the effectiveness of drug therapy in patients with functional ischemia of the lower extremities (FILE).

Patients and research methods

The examined group of patients

The prospective clinical trial included patients with FILE who were treated on an outpatient basis at the Clinic of Vascular Surgery of the Clinical Center in Niš in the period from January 2020 to December 2020.

Respondents who were diagnosed with FILE for the first time were included in the research. The diagnosis was made on the basis of history, clinical examination, Doppler echosonography and/or MDCT angiography of the main arteries of the lower extremities.

The criteria for inclusion in the study encompassed patients with stage IIa and IIb disease according to Fontaine, who had PAD of the lower extremities verified by Doppler sonography or MDCT angiography (10). The criteria for exclusion from the study encompassed patients with: I, III and IV stage of PAD according to Fontaine, amputation of the lower extremities, ejection fraction ≤ 40%, chronic peritoneal dialysis and hemodialysis, malignancies and associated diseases that lead to impaired general condition and physical condition.

Methodology

The research protocol was approved by the Ethics Committee of the Faculty of Medicine in Niš (12-15637-2/5 dated 12/24/2019). The research was fully adapted to the Declaration of Helsinki on ethical behavior and conducted according to the principles of Good Clinical Practice (GCP).

The classification of the disease stage was performed according to Fontaine: I stage (asymptomatic); IIa stage (moderate CD > 200 m); IIb stage (moderate to severe CD < 200 m); III stage (ischemic pain at rest, CD up to 50 m) and IV stage (presence of ulceration and gangrene). Patients with Fontaine stage IIa and IIb disease were included in the study.

Claudication distance

In order to obtain reproducible results, patients were given guidelines on how to measure the claudication distance. Subjects were advised to walk at a constant frequency and speed for a certain distance to obtain an objective assessment of step frequency (number of steps) and walking speed. The values of the claudication distance were determined based on the distance covered by the subject, expressed by the number of steps using the following model:

If a person walks at a constant speed v and frequency f for a given distance s with the number of steps n in a time period t, then the walking frequency can be calculated by the following formula (11):

$$Frequency: f = n/t$$
$$Walking\ speed: v = s/t$$
$$Step\ length: sl = s/n$$

Bearing in mind that the length of steps in men and women is different, it is necessary to introduce the following correction factor in the scale with the height of the examinee:

-Men step length (MSL) = 0.415 x height in cm

-Women step length (WSL) = 0.413 x height in cm

From the mentioned formulas, it follows that the length of the traveled path can be calculated as follows:

-Claudication distance (CD) = MSL or WSL x n

The claudication distance of the patients (expressed in meters) was determined and compared at the first examination and control examinations after three and six months after the introduction of drug therapy, whereby the values of the change/extension of the claudication distance (CCD) were obtained.

Groups of participants

Groups were formed based on the applied therapeutic modalities and the presence/absence of smoking habits in a ratio of 1 to 1.

Based on the applied drug therapy, the first group consisted of patients who received pentoxifylline 400 mg three times a day and acetylsalicylic acid (ASA) 100 mg once a day (pentoxifylline + ASA) and the second group consisted of patients who received cilostazol 100 mg twice a day and acetylsalicylic acid 100 mg once a day (cilostazol + ASA).

Statistical data processing

Statistical analysis was performed using the SPSS 16.0 software package for Windows. Methods of descriptive and analytical statistics were used. Continuous variables were described as average value ($\bar{X}$) and standard deviation (SD), while proportions (percentages) were used for categorical variables. The normality of the distribution was assessed by the Kolmogorov-Smirnov test, while the homogeneity of the distribution was tested by the Levin test. The assessment of the significance of the difference for continuous variables, with a normal distribution, was performed using parametric methods. The t-test for independent samples was used to compare two groups of respondents, and one-way ANOVA was used for three or more groups, while the Chi-square test was used for non-parametric variables. The difference is marked as significant if $p < 0.05$. In the case of a statistically significant difference, Tukey's HSD test was used. Spearman's correlation was used to assess the correlation.

Results

The study included 82 patients diagnosed with FILE treated at the Clinic of Vascular Surgery of the Clinical Center in Niš, starting from January 2020 to December 31, 2020. Smoking was present in 76.82% of respondents. In the research conducted, 48.78% of respondents used pentoxifylline + ASA, while 51.22% of respondents were treated with cilostazol + ASA

CD (claudication distance) values in relation to the choice and duration of drug therapy are shown in Table 1.

The results of the analyzed therapeutic modalities showed that there was no statistically significant difference in CD values after three months from the therapy introduction ($F(1.79) = 0.82$; $p = 0.37$; partial eta square = 0.1). Analysis of CD 6 months after the introduction of therapy found a statistically significant difference between the analyzed drug therapies ($F(1.79) = 5.06$; $p = 0.027$; partial eta squared = 0.6), the extension of the claudication distance was significantly greater in the group of patients who used cilostazol + ASA.

The influence of smoking and applied therapy on CCD is shown in Table 2.

In the group of subjects who did not smoke, there was no statistically significant CCD in relation to the applied therapy ($t(17) = 0.19$, $p = 0.85$; MD = -7.95; 95% CI: -94.76 to 78 .85; $\eta 2 < 0.01$) at the follow-up examination after 3 months. Static significance was not found even after 6 months of therapy initiation ($t(17) = 0.02$, $p = 0.98$; MD = -71.25; 95% CI: -346.46 to 203.96; $\eta 2 < 0.01$). At the follow-up examination after 3 months in smokers, there was no statistically significant CCD in relation to the applied therapy ($t(61) = 0.85$, $p = 0.40$; MD = -12.83; 95% CI: -43.05 to 17.38; $\eta 2 = 0.01$). Also, static significance was not found even after 6 months of therapy initiation ($t(61) = 2.48$, $p = 0.016$; MD = -63.28; 95% CI: -114.33 to -12.23; $\eta 2 = 0.09$).

The influence of the number of cigarettes/day and the applied therapy on CCD is shown in Table 3.

Table 1. CD values in relation to the choice and duration of drug therapy (m)

	Cilostazol + ASA			Pentoxifylline + ASK		
	N	$\bar{X}$	SD	N	$\bar{X}$	SD
First review	42	203.10	57.66	40	200.25	71.09
After 3 months	42	265.24	113.05	40	249.00	113.35
After 6 months	42	367.98 *	168.28	40	310.13*	162.82

*$p < 0.05$

Table 2. Influence of smoking and applied therapy on prolongation of claudication distance (m)

	ASA + pentoxifylline			ASA + cilostazol		
	N	$\bar{X}$	SD	N	$\bar{X}$	SD
Non-smokers						
After 3 months	8	72.50	91.77	11	80.45	86.21
After 6 months	8	222.50	130.69	11	220.91	167.45
Smokers						
After 3 months	32	42.81	55.73	31	55.65	64.04
After 6 months	32	81.72	102.72	31	145.00	99.82

Table 3. Influence of the number of cigarettes/day and applied therapy on the extension of the claudication distance (m)

	ASA + pentoxifylline			ASA + cilostazol		
	N	$\bar{X}$	SD	N	$\bar{X}$	SD
Smoking ≤ 20 cigarettes						
After 3 months	12	47.92	60.84	11	57.27	58.07
After 6 months	12	95.42	140.01	11	123.18	74.27
Smoking > 20 cigarettes						
After 3 months	20	39.75	53.84	20	54,75	68.55
After 6 months	20	73.50*	75.34	20	157.00*	111.37

*$p < 0.01$

In the group of subjects smoking ≤ 20 cigarettes/day, there was no statistically significant CCD in relation to the applied therapy ($t(21) = 0.38$, $p = 0.71$; MD = -9.36; 95% CI: -61 .04 to 42.33; $\eta 2 = 0.01$) at the follow-up examination after 3 months. Static significance was not found even after 6 months of initiation of therapy ($t(21) = 0.59$, $p = 0.56$; MD = -27.77, 95% CI: -126.34 to 70.81; $\eta 2 = 0.02$).

At the follow-up examination after 3 months in the group of subjects who smoked > 20 cigarettes/day, there was no statistically significant CCD in relation to the applied therapy ($t(38) = 0.77$, $p = 0.45$; MD = -15.00; 95% CI: -54.46 to 24.46; $\eta 2 = 0.02$). However, at the follow-up examination after 6 months, statistical significance was observed in terms of CCD between the analyzed groups ($t(38) = 2.78$, $p = 0.008$; MD = -83.50; 95% CI: -144.37 to -22 .63; $\eta 2 = 0.17$), significantly higher efficiency was achieved in the group of subjects who applied cilostazol + ASA.

The influence of length of smoking experience and applied therapy on CCD is shown in Table 4.

Table 4. Influence of the length of smoking experience and applied therapy on the extension of the claudication distance (m)

	ASA + pentoxifylline			ASA + cilostazol		
	N	$\bar{X}$	SD	N	$\bar{X}$	SD
Smoking duration ≤ 20 years						
After 3 months	8	63.13	93.46	5	77.00	79.73
After 6 months	8	137.50	174.03	5	164.00	91.41
Smoking duration > 20 years						
After 3 months	2	36.04	36.56	26	51.54	61.61
After 6 months	2	63.13*	59.67	26	141.35*	102.64

In the group of subjects with smoking experience ≤ 20 years, there was no statistically significant CCD in relation to the applied therapy ($t(11) = 0.27$, $p = 0.79$; MD = -13.88; 95% CI: -125 .19 to 97.44; $\eta 2 = 0.01$) at the follow-up examination after 3 months. Static significance was not found even after 6 months of therapy initiation ($t(11) = 0.31$, $p = 0.76$; MD = -26.50; 95% CI: -213.92 to 160.92; $\eta 2 = 0.01$).

At the follow-up examination after 3 months, in the group of subjects who smoked > 20 years, there was no statistically significant CCD in relation to the applied therapy ($t(48) = 1.07$, $p = 0.29$; MD = -15.50; 95% CI: -44.62 to 13.62; $\eta 2 = 0.02$). However, at the follow-up examination after 6 months, statistical significance was observed in terms of CCD between the analyzed groups ($t(48) = 1.07$, $p = 0.002$; MD = -78.22; 95% CI: -126.49 to -29 .95; $\eta 2 = 0.18$), significantly higher efficiency achieved in the group of subjects who applied cilostazol + ASA.

Discussion

The role of smoking in the etiopathogenesis of PAD has been known for more than a hundred years. Although the effects of smoking as a risk factor have been studied mostly in coronary artery disease (CAD), studies have shown a greater significance in the development of PAD compared to CAD. Smoking, together with diabetes, is the most significant risk factor for PAD, with a 4 times higher incidence compared to the non-smoking population (12). The study by He et al. showed the association of PAD with smoking, with a ratio of 1.5:1 in favor of smokers. Also, this research showed that quitting smoking for more than 10 years significantly reduced the risk of PAD, practically eliminating it (13). Tobacco smoke contains thousands of substances that can have toxic effects on health. The substances that attract the most attention of researchers are nicotine and carbon monoxide. The pathophysiological mechanisms by which nicotine and carbon monoxide lead to the development of atherosclerosis and PAD are numerous (14).

These substances lead to: endothelial dysfunction, increased adhesion of leukocytes and aggregation of platelets to the endothelium, increased triglycerides and LDL, insulin resistance, increased activity of fibrinogen, increased expression of tissue factor, vasoconstriction and increased oxidative stress. In addition, these toxic substances increase the adhesion of monocytes to endothelial cells, which is one of the first steps in the development of atherosclerosis (15).

The results of the research show that in relation to the therapeutic modalities, there was no statistically significant difference in CCD at the follow-up examinations in the group of non-smokers and smokers. However, the research shows that at the follow-up examination after 6 months, the number of cigarettes/day and the length of smoking experience had a statistically significant effect on CCD in relation to the applied therapeutic modalities, noting that cilostazol + ASA was more effective than pentoxifylline + ASA in the group of subjects who smoke > 20 cigarettes/day ($p < 0.01$) and who smoke for > 20 years ($p < 0.01$).

These results can largely be explained by the proven effects of cilostazol on improving the endothelium-dependent vasodilator response in smokers (16). A randomized prospective study on patients implanted with a drug-eluting stent

showed that cilostazol eliminated the negative impact of smoking on adverse outcomes after stent implantation. One of the main conclusions of the study was that smokers who were treated with cilostazol and dual antiplatelet therapy had a similar outcome to non-smokers, while in the group of patients treated only with dual antiplatelet therapy, the outcome was significantly better in non-smokers. That is to say, that smoking stimulates the antiplatelet effects of cilostazol. The main pharmacologically active metabolites of cilostazol are formed in the body through cytochrome P450 (CYP3A4 and CYP 2C19). Bearing in mind that there is very little data on the influence of smoking on the pharmacokinetics of cilostazol, it can be assumed that nicotine can lead to inhibition of metabolism and an increase in the concentration of active metabolites of cilostazol in plasma (17). Cilostazol increases the endothelium-dependent vasodilatation of the brachial artery after artificial ischemia by up to 50% in smokers (18). Similar effects were shown for the femoral artery (19). An experiment on rats was conducted where the rats were divided into three groups: treated with cilostazol, aspirin and a control group. Rats were exposed to nicotine smoke for one minute and one hour after, the pial blood vessels were observed. It was confirmed that there was nicotine-induced constriction of blood vessels in the group treated with aspirin and in the control group, while vasoconstriction was absent in the group treated with cilostazol (20).

Smoking and PAD are closely related. A meta-analysis of 17 studies showed a 2.2-fold higher prevalence of symptomatic PAD in smokers compared to nonsmokers (21). Smoking accelerates the progression of PAD and leads to the progression of stable claudication to symptoms of critical lower limb ischemia (22). Yataco and Gardner investigated the acute effects of smoking on the reduction of the AB index in chronic smokers with PAD. The research included 10 chronic smokers who had smoking and non-smoking days. The non-smoking day meant that the patients refrained from smoking and caffeinated drinks 12 hours before the test, and the smoking day meant smoking two filter cigarettes 10 minutes before the test. After the analysis of the obtained ABI values, significantly higher values were proven, during the non-smoking day (23). The influence of smoking on the occurrence of PAD is proportional to the number of cigarettes consumed, so those who smoke 30 or more cigarettes per day have a significantly higher incidence of PAD than those who smoke up to 10 cigarettes, regardless of gender and age. Also, the length of smoking experience was significantly associated with the risk of developing PAD (24). Research by Lassil et al. showed a direct correlation between the number of cigarettes consumed and the frequency of amputations in patients with PAD. The frequency of amputations has been proven to be 21% in heavy smokers, compared to about 2% in moderate smokers (25).

On the other hand, it is necessary to look at the protective effects that cilostazol can achieve at the level of the cardiovascular system in the case of the presence of the nicotine effect (26). Therefore, its application in smokers with PAD may be justified in order to inhibit adverse events caused by cigarette consumption.

Conclusion

The number of cigarettes/day and length of smoking experience have a significant effect on the applied therapeutic modality in patients with PAD. Cilostazol + ASA therapy was more effective than pentoxifylline + ASA therapy in the group of smokers who had smoked > 20 cigarettes/day for > 20 years.

References

1. Criqui MH, Aboyans V. Epidemiology of peripheral artery disease. Circ Res 2015; (9): 1509-26. [CrossRef] [PubMed]
2. Skórkowska-Telichowska K, Kropielnicka K, Bulińska K, Pilch U, Woźniewski M, Szuba A et al. Insufficient modification of atherosclerosis risk factors in PAD patients. Adv Clin Exp Med 2018; 27(6): 819-26. [CrossRef] [PubMed]
3. van Kuijk JP, Flu WJ. Long-term prognosis of patients with peripheral arterial disease with or without polyvascular atherosclerotic disease. Eur Heart J 2010; 31(8):992-9. [CrossRef] [PubMed]
4. Farber A, Eberhardt RT. The Current State of Critical Limb Ischemia: A Systematic Review. JAMA Surg 2016;151(11):1070-1077. [CrossRef] [PubMed]
5. Dawson DL. Comparative effects of cilostazol and other therapies for intermittent claudication. Am J Cardiol 2001;87(12A):19D-27D. [CrossRef] [PubMed]
6. Hiatt WR, Money SR, Brass EP. Long-term safety of cilostazol in patients with peripheral artery disease: the CASTLE study (Cilostazol: A Study in Long-term Effects). J Vasc Surg 2008; 47(2): 330-6. [CrossRef] [PubMed]
7. Meijer WT, Hoes AW, Rutgers D, Botts ML, Hoffman A, Grobbee DE. Peripheral arterial disease in the elderly: the Rotterdam Study. Arteriosclerosis, thrombosis, and vascular biology 1998; 18(2): 185-92. [CrossRef] [PubMed]
8. Hamburg NM, Balady GJ. Exercise rehabilitation in peripheral artery disease: functional impact and mechanisms of benefits. Circulation 2011; 123(1): 87-97. [CrossRef] [PubMed]
9. Willigendael EM, Teijink JA, Bartelink ML, Peters RJ, Büller HR, Prins MH. Smoking and the patency of lower extremity bypass grafts: a meta-analysis. J Vasc Surg 2005; 42(1): 67-74. [CrossRef] [PubMed]
10. Fontaine R, Kim M, Kieny R. Surgical treatment of peripheral circulation disorders. Helv Chir Acta 1954; 21(5–6): 499–533. [PubMed]
11. de Silvaa A, Sampatha W, Sameeraa N, Amarasinghea Y, Mitanib A. Development of a novel telecare system, integrated with plantar pressure measurement system. Informatics in Medicine Unlocked 2018, 12: 98–105.
12. Price JF, Mowbray PI, Lee AJ, Rumley A, Lowe GD, Fowkes FG. Relationship between smoking and cardiovascular risk factors in the development of peripheral arterial disease and coronary artery disease: Edinburgh Artery Study. Eur Heart J 1999; 20(5): 344-53. [CrossRef] [PubMed]
13. He Y, Jiang Y, Wang J, Fan L, Li X, Hu FB. Prevalence of peripheral arterial disease and its association with smoking in a population-based study in Beijing, China. J Vasc Surg 2006; 44(2): 333-8. [CrossRef] [PubMed]
14. Siasos G, Tsigkou V, Kokkou E, Oikonomou E, Vavuranakis M, Vlachopoulos C, et al Smoking and atherosclerosis: mechanisms of disease and new therapeutic approaches. Curr Med Chem 2014; 21(34): 3936-48. [CrossRef] [PubMed]
15. Adams MR, Jessup W, Celermayer DS. Cigarette smoking is associated with increased human monocyte adhesion to endothelial cells: reversibility with oral L-arginine but not vita-min C. J Am Coll Cardiol 1997; 29: 491–7. [CrossRef] [PubMed]
16. Kim KS, Park HS, Jung IS, Park JH, Ahn KT, Jin SA, Park YK, Kim JH, Lee JH, Choi SW, Jeong JO, Seong IW. Endothelial dysfunction in smokers can be improved with oral cilostazol treatment. J Cardiovasc Ultrasound 2011;19(1):21-5. [CrossRef] [PubMed]
17. Kim HL, Suh JW, Lee SP, Kang HJ, Koo BK, Cho YS, et al. Cilostazol eliminates adverse smoking outcomes in patients with drug-eluting stent implantation. Circ J 2014; 78(6): 1420-7. [CrossRef] [PubMed]
18. Oida K, Ebata K, Kanehara H, Suzuki J, Miyamori I. Effect of cilostazol on impaired vasodilatory response of the brachial artery to ischemia in smokers. J Atheroscler Thromb 2003; 10(2):93-8. [CrossRef] [PubMed]
19. Yasuda K, Sakuma M, Tanabe T. Hemodynamic effect of cilostazol on increasing peripheral blood flow in arteriosclerosis obliterans. Arzneimittel-forschung 1985; 35: 1198-200. [PubMed]
20. Iida H, Iida M, Takenaka M, Fukuoka N, Dohi S. Comparative effects of cilostazol and aspirin on the impairment of endothelium-dependent cerebral vasodilation caused by acute cigarette smoking in rats. J Thromb Thrombolysis 2010; 29(4):483-8. [CrossRef] [PubMed]
21. Willigendael EM, Teijink JA, Bartelink ML, Kuiken BW, Boiten J, Moll FL, et al. Influence of smoking on incidence and prevalence of peripheral arterial disease. J Vasc Surg 2004; 40(6): 1158-65. [CrossRef] [PubMed]
22. Chi YW, Jaff MR. Optimal risk factor modification and medical management of the patient with peripheral arterial disease. Catheter Cardiovasc Interv 2008; 71(4): 475-89. [CrossRef] [PubMed]
23. Yataco AR, Gardner AW. Acute reduction in ankle/brachial index following smoking in chronic smokers with peripheral arterial occlusive disease. Angiology 1999; 50(5): 355-60. [CrossRef] [PubMed]
24. Cole CW, Hill GB, Farzad E, Bouchard A, Moher D, Rody K, et al. Cigarette smoking and peripheral arterial occlusive disease. Surgery. 1993; 114(4): 753-6; discussion 756-7. [PubMed]
25. Lassila R, Lepäntalo M. Cigarette smoking and the outcome after lower limb arterial surgery. Acta Chir Scand 1988; 154(11-12): 635-40. [PubMed]
26. Wang SY, Ni X, Hu KQ, Meng FL, Li M, Ma XL, et al. Cilostazol alleviate nicotine induced cardiomyocytes hypertrophy through modulation of autophagy by CTSB/ROS/p38MAPK/JNK feedback loop. Int J Biol Sci 2020; 16(11): 2001-13. [CrossRef] [PubMed]

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EFIKASNOSTI MEDIKAMENTOZNE TERAPIJE BOLESNIKA SA PERIFERNOM ARTERIJSKOM BOLEŠĆU U ZAVISNOSTI OD PUŠAČKIH NAVIKA

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Periferna arterijska bolest (engl. *peripheral arterial disease* – PAD) jeste jedna od manifestacija ateroskleroze, koja se manifestuje prvenstveno u perifernim arterijama donjih ekstremiteta i aorto-ilijakalnog segmenta. Najveći broj bolesnika, oko 90% njih, ima funkcionalnu ishemiju (Stadijum IIa i IIb prema Fontaineu). Terapija izbora za ove bolesnike sastoji se od kombinacije acetilsalicilne kiseline, cilostazola i pentoksifilina. Pušenje je veoma značajan faktor rizika za razvoj PAD-a i, takođe, jedan od najznačajnijih modifikatora ishoda lečenja. Studijom su obuhvaćena 82 bolesnika sa dijagnozom ishemije donjih ekstremiteta (FIDE) lečena na Klinici za vaskularnu hirurgiju Kliničkog centra u Nišu u periodu od januara do 31. decembra 2020. godine. Pušači su činili 76,82% ispitanika. U sprovedenom istraživanju, 48,78% ispitanika koristilo je pentoksifilin + acetilsalicilnu kiselinu, dok su 51,22% ispitanika lečena cilostazolom + acetilsacilnom kiselinom. Rezultati su pokazali da je produženje klaudikacione distance nakon šest meseci bilo značajno veće u grupi bolesnika koji su koristili cilostazol + acetilsalicilnu kiselinu. U podgrupi bolesnika koji su pušili više od 20 cigareta dnevno i duže od 20 godina došlo je do značajnijeg povećanja klaudikacione distance nakon šest meseci u grupi koja je koristila cilostazol + acetilsalicilnu kiselinu u poređenju sa grupom pentoksifilin + acetilsalicilna kiselina. Dakle, broj cigareta na dan i dužina pušenja imaju značajan uticaj na primenjeni terapijski modalitet kod bolesnika sa PAD-om. Terapija cilostazol + acetilsalicilna kiselina bila je efikasnija od terapije pentoksifilin + acetilsalicilna kiselina.

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Ključne reči: *periferna arterijska bolest, lečenje, pušenje*