Original article

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IMPORTANCE OF RISK FACTORS IN THE EFFECTIVENESS OF MEDICATION THERAPY IN PATIENTS WITH FUNCTIONAL LOWER EXTREMITY ISCHEMIA

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Analysis of the influence of risk factors on drug therapy measured by prolongation of the claudication distance in patients with functional lower extremity ischemia (FLEI) can significantly improve the individual approach to the treatment of these patients.

The aim of the study was to determine the impact of risk factors on the effectiveness of medicament therapy in patients with FLEI.

The study included 82 patients with diagnosed FLEI (Fontaine IIa, IIb), treated at the Clinic for Vascular Surgery of the University Clinical Center in Niš, starting from January 2020 to December 31, 2020.

After 6 months of examination, there was a statistically significant difference in the prolongation of claudication distance in relation to the therapeutic modality in woman (p = 0.03), patients with dyslipidemia (p = 0.001) and patients with hypertension (p = 0.02), noting that higher efficacy was achieved in the group of respondents who used cilostazol and acetylsalicylic acid (ASA).

Risk factors that have a significant effect on the applied therapeutic modality are female gender, dyslipidemia and hypertension, while age, obesity and male gender are risk factors where such correlation is not present. Cilostazol and ASA therapy were more effective than pentoxifylline and ASA therapy in the group of respondents suffering from hypertension and dyslipidemia as well as in women.

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Introduction

Peripheral arterial disease (PAD) is a manifestation of systemic atherosclerosis with an increase in the prevalence of aging population, caused by a number of predisposing factors. Risk factors for coronary, renovascular, cerebrovascular and peripheral arterial disease are identical. Chronic progression, development and complications of atherosclerotic lesions or plaques are accelerated by risk factors such as gender, age, hereditary factors, smoking, hypertension, hyperlipidemia, chronic renal failure, obesity, diabetes, physical inactivity, inadequate diet and emotional stress (1).

Medicament therapy that is approved and has shown efficient in relieving the symptoms and prolongation of claudication distance involves the use of phosphodiesterase inhibitors, pentoxifylline and cilostazol (2, 3). In addition, the use of antithrombotic medicaments is a significant component in the treatment of PAD. The use of acetylsalicylic acid (ASA) and clopidogrel slows progression, reduces the percentage of graft occlusion after revascularization and reduces the risk of cardiovascular death by 25% in patients with PAD (4).

Peripheral vasodilators represent a potentially useful group of medicaments in the treatment of PAD (4). Pentoxifylline is a theophylline derivative with significant hemorrhoidal properties.

It can reduce the symptoms of claudication by decreasing blood viscosity and increasing the deformability of erythrocytes and leukocytes (5). However, the available guidelines for the treatment of PAD favor the use of cilostazol recommending IA in the treatment of symptomatic claudication (6).

Regarding the complexity of the occurrence, the impact of various risk factors and the progression of peripheral arterial disease, this prospective study aims to determine the relationship between the impacts of risk factors on the effectiveness of medicament therapy in patients with functional lower extremity ischemia (FLEI).

Patients and research methods

Patient group examined

The prospective clinical trial included patients with FLEI 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.

The study included subjects who were first diagnosed with FLEI. The diagnosis was made according to anamnesis, clinical examination, dopplerechosonography and/or MSCT angiography of the main arteries of the lower extremities.

The criteria applied for inclusion in the study involved: patients with stage IIa and IIb disease according to Fontaine, in whom PAD of the lower extremities had been verified using Doppler sonography or MSCT angiography (7).

The criteria applied for exclusion from the study involved patients with I, III and IV stage PAD according to Fontaine, amputation of the lower extremities, ejection fraction ≤ 40%, chronic peritoneal dialysis and hemodialysis, malignancies and associated diseases leading to impaired general condition and physical fitness.

Methodology

The research protocol was approved by the Ethics Committee of the Faculty of Medicine in Niš (12-15637-2/5 dated December 24, 2019). The research completely comes to terms with the Helsinki Declaration on Ethical Treatment and it was conducted according to the principles of Good Clinical Practice (GCP). All patients were informed of the purpose of the study and they voluntarily signed a consent form. The research was designed in the form of a prospective cross-sectional study using a survey.

The investigation included a questionnaire with closed answers and different variants from dichotomous to combined, with open additional questions.

The classification of the respondents' disease stage was performed according to Fontaine: Stage I (asymptomatic); Stage IIa (moderate claudication distance (CD) > 200 m); Stage IIb (moderate to severe CD < 200 m); Stage III (ischemic pain at rest, CD up to 50 m) and stage IV (presence of ulceration and gangrene).

Claudication distance

In order to obtain reproducible results, the patients were given guidelines on how to measure claudication distance. The respondents were recommended to walk at a constant frequency and speed for a certain distance in order to obtain an objective assessment of step frequency (number of steps) and walking speed. The values of claudication distance were determined on the basis of the distance the respondents had traveled, 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 the time period **t**, then the walking frequency can be calculated according to the following formula (8, 9):

Walking frequency: $f = \frac{n}{t}$

Walking speed: $v = \frac{s}{t}$

Step length: $sl = \frac{s}{n}$

Taking into account that step length differs between men and women, it is necessary to introduce the following correction factor in accordance with the height of respondents:

Step length in men (cm) = sl_m = 0.415 x height (cm)

Step length in women (cm) = sl_w = 0.413 xheight (cm)

The above formulas show that the length of the traveled distance can be calculated in the following way:

Traveled distance $= s = sl \; x \; n$

Traveled distance in men (m) = sl_m x n $= \frac{0.415 \; x \; height \; (cm) \; x \; number \; of \; steps}{100}$

Traveled distance in women (m) = sl_w x n = $\frac{0.413 \; x \; height \; (cm) \; x \; number \; of \; steps}{100}$

The claudication distance (CD) of the patients (expressed in meters) was determined and compared at the first examination, and control examinations after three and six months starting from the introduction of medicament therapy.

The differences in the obtained values of claudication distance in the indicated periods determined the prolongation of claudication distance (PCD) values.

Respondent groups

In order to perform an adequate data analysis based on demographic characteristics, therapeutic modalities, risk factors and physical activity, the following respondent groups were formed:

- gender: male and female respondents;
- age: < 65 years and ≥ 65 years;
- medicament therapy:
- the first group included the patients administered pentoxifylline 400 mg three times a day and acetyl-salicylic acid 100 mg once a day (pentoxifylline and ASA);
- the second group included the patients administered cilostazol 100 mg twice a day and acetyl-salicylic acid 100 mg once a day (cilostazol and ASA);
- presence/absence of risk factors: smoking, obesity, diabetes, dyslipidemia and hypertension,

Determination of body mass index (BMI) was performed by a calculation based on the following formula: BMI = body weight (BW)/body height $(BH)^2$. The patients were considered obese if their BMI was over 30 kg/m^2.

The presence of diabetes, dyslipidemia and hypertension was established by adequate specialist and subspecialist branches of medicine.

Statistical data processing

The statistical analysis was performed with the software package SPSS 16.0 for Windows. The methods included descriptive and analytical statistics. Continuous variables were described as mean (X) and standard deviation (SD), while proportional percentages were used for category variables. The normality of distribution was assessed by the Kolmogorov-Smirnov test, while the homogeneity of distribution was tested by the Levin test. The significance of the difference for continuous variables, with normal distribution, was estimated by 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 nonparametric variables. The difference was marked significant if $p < 0.05$. In the case of a statistically significant difference, the Tukey HSD test was used. Spearman's correlation was used to estimate the correlation.

Results

The study included 82 patients diagnosed with FLEI treated at the Clinic for Vascular Surgery of the Clinical Center in Niš, starting from January 2020 to December 31st, 2020. In the conducted research, 48.78% of the subjects used pentoxifylline and ASA, while 51.22% of the respondents were treated with cilostazol and ASA.

The basic demographic characteristics of patients and risk factors are shown in Tables 1 and 2.

Of the total number of the examined patients, 49 (59.76%) were male and 33 (40.24%) were female. The average age of the respondents was 67.62 years (SD = 8.22). The youngest respondent was 48, and the oldest was 82 years old.

In the largest number of patients with FLEI, smoking was the most common risk factor (76.82%), followed by hypertension (75.60%), while dyslipidemia was the least common (63.71%).

The values of CD in relation to the choice and duration of medicament therapy are shown in Table 3.

One-factor analysis of covariance compared the effectiveness of applied therapeutic modalities on CD values between the first and control examinations after 3 and 6 months. The independent variable was the type of therapy (cilostazol and ASA and pentoxifylline and ASA), and the dependent variables were CD values after 3 and 6 months. The results of CD at the first examination were used as a covariate in the analysis, Preliminary checks established that the assumptions about normality, linearity of variance homogeneity, regression slope homogeneity and covariate measurement reliability were not violated.

The results of the analyzed therapeutic modalities showed that there was no statistically significant difference in the values of CD three months after the therapy had been introduced ($F(1.79) = 0.82$; $p = 0.37$; partial eta square = 0.1). CD analysis 6 months after the therapy had been introduced showed a statistically significant difference between the analyzed medicament therapy ($F(1, 79) = 5.06$; $p = 0.027$; partial eta square = 0.6), whereas the prolongation of claudication distance was greater in the group of patients who received cilostazol and ASA.

In order to examine the relationship between risk factors and the effectiveness of medicament therapy in patients with FLEI, the correlation of PCD patients with the following risk factors was analyzed: gender, age, obesity, diabetes, dyslipidemia, hypertension and the number of risk factors.

Table 1. Demographic characteristics of patients

Gender	N	%
Male	49	59.76
Female	33	40.24
Age		
< 65	29	35.37
≥ 65	53	64.63
Total	82	100

Table 2. Risk factors of patients

Factor	N	%
Obesity	59	71.95
Diabetes	57	69.51
Dyslipidemia	52	63.71
Hypertension	62	75.60

Table 3. Values of CD in relation to the choice and duration of medicament therapy (m)

	Cilostazol + ASA			Pentoxifylline + ASK		
	N	$\overline{X}$	SD	N	$\overline{X}$	SD
First examination	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

Table 4. Influence of risk factors and applied therapy on PCD (m)

Gender	Pentoxifylline + ASK			Cilostazol + ASA		
	N	$\overline{X}$	SD	N	$\overline{X}$	SD
Male						
After 3 months	23	60.43	76.91	26	56.92	67.26
After 6 months	23	133.48	145.51	26	171.73	127.40
Female						
After 3 months	17	32.94	38.20	16	70.63	76.33
After 6 months	17	77.94*	69.60	16	153.75*	120.31
Age	Pentoxifylline + ASK			Cilostazol + ASA		
	N	$\overline{X}$	SD	N	$\overline{X}$	SD
< 65 years						
After 3 months	15	71.33	88.77	14	101.07	89.85
After 6 months	15	142.00	171.44	14	247.86	154.88
≥ 65 years						
After 3 months	25	35.20	39.96	28	42.68	49.28
After 6 months	25	90.60	75.61	28	123.39	79.28
Obesity	Pentoxifylline + ASK			Cilostazol + ASA		
	N	$\overline{X}$	SD	N	$\overline{X}$	SD

< 30 kg/m²						
After 3 months	12	93.33	79.61	11	134.09	87.52
After 6 months	12	197.08	147.01	11	292.27	154.68
≥ 30 kg/m²						
After 3 months	28	29.64	45.99	31	36.61	40.26
After 6 months	28	72.50	87.22	31	119.68	69.52
Diabetes	Pentoxifylline + ASK			Cilostazol + ASA		
	N	$\overline{X}$	SD	N	$\overline{X}$	SD
Without diabetes						
After 3 months	12	47.08	62.61	13	85.00	86.29
After 6 months	12	146.67	122.54	13	210.77	144.08
With diabetes						
After 3 months	28	49.46	66.03	29	51.90	60.70
After 6 months	28	94.11	119.43	29	144.31	109.77
Dyslipidemia	Pentoxifylline + ASK			Cilostazol + ASA		
	N	$\overline{X}$	SD	N	$\overline{X}$	SD
Without dyslipidemia						
After 3 months	17	79.12	82.12	13	116.15	92.65
After 6 months	17	170.88	159.77	13	257.69	167.33
With dyslipidemia						
After 3 months	23	26.30	34.19	29	37.93	39.83
After 6 months	23	64.78**	50.01	29	123.28**	67.60
Hypertension	Pentoxifylline + ASK			Cilostazol + ASA		
	N	$\overline{X}$	SD	N	$\overline{X}$	SD
Without hypertension						
After 3 months	11	57.27	82.23	9	108.89	106.32
After 6 months	11	174.09	144.77	9	241.67	195.46
With hypertension						
After 3 months	29	45.52	57.37	33	49.39	52.11
After 6 months	29	85.52*	103.74	33	143.94*	88.91

Discussion

At the first examination, the values of claudication distance between the groups of patients who received pentoxifylline and ASA and cilostazol and ASA were not significantly different in terms of statistics. Also, the results show that there was no statistically significant difference in the values of CD three months after the introduction of therapy between the analyzed therapeutic modalities. CD analysis 6 months after the introduction of therapy revealed a statistically significant difference ($p < 0.05$) between the treatment modalities, noting that the prolongation of claudication distance was greater in the group of patients who received cilostazol and ASA compared to the group of patients who received pentoxifylline and ASA.

The first clinical study to compare the efficacy of pentoxifylline and cilostazol in the treatment of intermittent claudication was conducted by Dawson et al. The study included 698 patients with intermittent claudication, and the efficacy and safety were monitored for 24 weeks. At the end of the observed period, the group of patients who used cilostazol, achieved significantly better PCD results, compared to the group of patients who used pentoxifylline (94 m vs. 74 m) (10). Singh et al. came to similar observations in their research conducted in India. Namely, the therapeutic effects of pentoxifylline and cilostazol were monitored in 79 patients with PAD for 12 weeks with a pronounced superior effect on PCD in the group of respondents who used cilostazol (11). The higher efficacy of cilostazol in relation to pentoxifylline was also noticed in research conducted by Gupta et al. (12). The study conducted in the United Kingdom also highlighted the advantage of cilostazol over pentoxifylline in the treatment of PAD from a

pharmacoeconomic aspect (13). The obtained results of the conducted research match the results of the previously mentioned studies. The unique combination of antiplatelet, vasodilatory and antiproliferative effects of cilostazol makes it a preferable medicament for FILE therapy. Long-term use of cilostazol did not show significant differences in the frequency of bleeding or cardiovascular and cerebrovascular complications compared to the use of pentoxifylline (14). The results of the research conducted so far suggest that cilostazol will be an inevitable therapeutic option for reducing the symptoms and improving the quality of life in patients with intermittent claudication (15).

Recent research indicates that women suffer from this chronic disease almost as frequently as men, taking into account the phenomenon of the twentieth century (women live longer and make greater part of the elderly population) (16, 17). Accordingly, the main goals of treatment of peripheral arterial disease are similar for both genders and they relate to reducing morbidity/mortality, reducing the symptoms and improving the quality of life (18). The research results indicate that there was no statistically significant difference in terms of PCD at follow-up examinations after 3 and 6 months in relation to respondents' gender. The research results indicate that in women, at the follow-up examination after 6 months, there was a statistically significant difference ($p < 0.05$) in PCD between the applied therapeutic modalities, noting that higher efficacy was achieved in the group of respondents who used cilostazol and ASA in relation to the group of respondents who used pentoxifylline and ASA. There are very few available studies that have compared the efficacy of medicament therapy in relation to respondents' gender. In their study, Pande et al. confirmed that there was no statistically significant difference in the efficacy of medicament therapy in relation to respondents' gender, which matches the results of this study (19). However, in contrast to medicament therapy, the results of a study conducted by Gallagher et al. have shown that the endovascular approach in the treatment of individual lesions that lead to critical ischemia of lower extremities has more effective results in women, and the choice should be adjusted to respondents' gender (20).

In relation to the applied therapeutic modalities, there was no statistically significant difference in PCD at control examinations in the group of respondents under the age of 65 and the group of respondents over the age of 65. The results of the research are in accordance with previously conducted studies in which the efficacy of pentoxifylline and cilostazol was confirmed regardless of the respondents' age (2, 21).

The results of the study indicate that in relation to therapeutic modalities, there was no statistically significant difference in PCD at follow-up examinations in the group of respondents with BMI $< 30 kg/m^2$ and the group of respondents with BMI $\geq 30 kg/m^2$. Previous studies did not take into account the impact of obesity on the outcome of PAD therapy, as obesity was the exclusion criterion in most cases. However, the antiatherogenic and anti-inflammatory potential of cilostazol could favor the use of this medication in obese patients with intermittent claudication. This is supported by the results of research conducted by Kim et al. showing that an eight-week administration of cilostazol contributes to a significant increase in lipoprotein lipase and inhibition of cytokine production (22). Further research in the field of investigating the effect of cilostazol in obese patients with intermittent claudication will confirm these assumptions.

Diabetes is one of the most important risk factors leading to PAD. Literature data indicate that the prevalence of PAD in diabetics over the age of 50 is about 30%, while in patients with critical limb ischemia, diabetes is present in more than 50% of cases (23). In relation to therapeutic modalities, there was no statistically significant difference between PCD at follow-up examinations in the group of patients with diabetes and the group of patients without diabetes. The therapy outcome in patients with diabetes mellitus and PAD depends on the interaction between factors such as comorbidities, the presence of infection, neuropathy and the immune response (24). Poor glycemic control is associated with a higher prevalence of PAD and the risk of adverse outcomes, as well as reduced success of therapy, both medication and surgical modalities (25).

Dyslipidemia is a variable risk factor in the development of PAD. It is a disorder that occurs as a result of accelerated synthesis or slow breakdown of lipoproteins involved in the transport of cholesterol and triglycerides in plasma. It is generally accepted that hyperlipoproteinemia is one of the most important independent risk factors for atherosclerosis and peripheral vascular disease (26). The results of the conducted research show that the presence of dyslipidemia had a statistically significant effect on the efficacy of medicament therapy. A statistically significant difference ($p < 0.01$) was found in the group of respondents suffering from dyslipidemia at the control examination after 6 months, noting that higher efficacy was achieved in the group of respondents who used cilostazol and ASA compared to the group of respondents who used pentoxifylline and ASK. Cilostazol is a medicament that, in addition to vasodilators and antithrombotic medicaments, also has significant effects at the level of atherogenic dyslipidemia. It is a medication that can improve the pro-atherogenic lipid profile in patients with PAD or diabetes by lowering serum triglycerides while

increasing HDL levels. In addition, cilostazol exerts its effect by acting on pro-atherogenic lipoproteins and apolipoproteins (27).

Hypertension is a factor that increases the risk of PAD by 2–3 times. In the conducted research, 75.6% of patients had both PAD and hypertension (28). In the group of respondents with hypertension, the results of the research indicate that at the control examination after 6 months there was a higher efficacy of cilostazol and ASA compared to pentoxifylline and ASA ($p < 0.05$).

Conclusion

According to the study results, it can be concluded that cilostazol and ASA therapy is more effective in prolonging claudication distance compared to pentoxifylline and ASA therapy in patients with functional ischemia of the lower extremities.

Risk factors that have a significant effect on the applied therapeutic modality are female gender, dyslipidemia and hypertension, while age, obesity and male gender are risk factors where such correlation is not present. Cilostazol and ASA therapy was more effective than pentoxifylline and ASA therapy in the group of respondents suffering from hypertension and dyslipidemia as well as in women.

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UTICAJ FAKTORA RIZIKA NA EFIKASNOST MEDIKAMENTOZNE TERAPIJE KOD BOLESNIKA SA FUNKCIONALNOM ISHEMIJOM DONJIH EKSTREMITETA

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Analiza uticaja faktora rizika na medikamentoznu terapiju, merena produženjem klaudikacione distance, kod bolesnika sa funkcionalnom ishemijom donjih ekstremiteta (FIDE) može značajno unaprediti individualni pristup u lečenju.

Cilj rada bio je da se utvrdi uticaj faktora rizika na efikasnost medikamentozne terapije kod bolesnika sa FIDE.

Istraživanjem su obuhvaćena 82 bolesnika sa dijagnostikovanom FIDE (Fontaine IIa, IIb) lečena na Klinici za vaskularnu hirurgiju Univerzitetskog kliničkog centra u Nišu u periodu od januara do 31. decembra 2020. godine.

Nakon šest meseci pregleda, uočena je statistički značajna razlika u produženju klaudikacione distance u odnosu na terapijski modalitet kod žena (p = 0,03), bolesnika sa dislipidemijom (p = 0,001) i bolesnika sa hipertenzijom (p = 0,02), uz napomenu da je veća efikasnost postignuta u grupi ispitanika koji su koristili cilostazol i acetilsalicilnu kiselinu (ASK).

Faktori rizika koji umnogome utiču na primenjeni terapijski modalitet jesu pripadnost ženskom polu, dislipidemija i hipertenzija; uzrast, gojaznost i pripadnost muškom polu faktori su rizika kod kojih navedena korelacija nije prisutna. Terapija cilostazolom i ASK-om bila je efikasnija od terapije pentoksifilinom i ASK-om u grupi ispitanika sa hipertenzijom i dislipidemijom, kao i kod žena.

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***Ključne reči**: faktori rizika, medikamentozna terapija, periferna arterijska bolest*