

**Original article**

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**THE IMPACT OF ALCOHOL CONSUMPTION ON THE EFFICACY OF  
PHARMACOLOGICAL THERAPY IN PATIENTS WITH PERIPHERAL ARTERIAL  
DISEASE**

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The exact pathogenetic mechanism of the association of alcohol with peripheral arterial disease (PAD) is still insufficiently clearly defined. Moderate alcohol consumption appears to reduce the risk of PAD, while excessive consumption increases it. The aim of the study was to determine the effect of alcohol on the effectiveness of drug therapy in patients with PAD. The

study included 82 PAD patients (Fontaine IIa, IIb), treated at the Clinic for Vascular Surgery of the University Clinical Center in Nis, starting from January 2020 to December 31, 2020. The results of the conducted research indicate a statistically significant more effective effect of cilostazol compared to pentoxifylline after 6 months of use in general ( $p < 0.05$ ) as well as in the group of patients who do not consume alcohol ( $p < 0.05$ ). There was no statistically significant difference in the effects of the applied therapeutic modalities in the group of subjects who consumed alcohol at the control examinations. The results of the study showed a statistically significant more favorable effect of cilostazol compared to pentoxifylline in general, as well as in the group of patients who do not consume alcohol, while alcohol consumption and the number of alcoholic beverages consumed by patients per week did not statistically significant affect the effectiveness of the applied therapeutic modalities in patients with PAD.

**Key words:** drug therapy, alcohol, peripheral arterial disease

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## **UTICAJ ALKOHOLA NA EFIKASNOST MEDIKAMENTOZNE TERAPIJE KOD PACIJENATA SA PERIFERNOM ARTERIJSKOM BOLEŠĆU**

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Tačan patogenetski mehanizam povezanosti alkohola sa perifernom arterijskom bolešću (PAB) još uvek nije dovoljno jasno definisan. Umerena konzumacija alkohola povezivana je sa smanjenjem rizik od PAB, dok je prekomerna konzumacija sa povećanjem. Cilj istraživanja bio je utvrditi uticaj alkohola na efikasnost terapije lekovima kod pacijenata sa PAB. U istraživanje je uključeno 82 pacijenta sa dijagnozom PAB (*Fontaine* IIa, IIb), lečenih na Klinici za vaskularnu hirurgiju Univerzitetskog kliničkog centra u Nišu, počev od januara 2020. do 31. decembra 2020. godine. Rezultati sprovedenog istraživanja ukazuju na statistički

značajno efikasniji efekat cilostazola u poređenju sa pentoksifilinom nakon 6 meseci upotrebe uopšte ( $p < 0,05$ ), kao i u grupi pacijenata koji ne konzumiraju alkohol ( $p < 0,05$ ). Nije bilo statistički značajne razlike u efektima primenjenih terapijskih modaliteta u grupi ispitanika koji su konzumirali alkohol na kontrolnim pregledima. Rezultati istraživanja pokazali su na statistički značajno povoljniji efekat cilostazola u poređenju sa pentoksifilinom uopšte, kao i u grupi pacijenata koji ne konzumiraju alkohol, dok konzumiranje alkohola i broj alkoholnih pića koje pacijent konzumira nedeljno nije statistički značajno uticao na efikasnost primenjenih terapijskih modaliteta kod pacijenata sa PAB.

**Ključne reči:** medikamentozna terapija, alkohol, periferna arterijska bolest

## Introduction

The exact pathogenetic mechanism of the correlation between alcohol consumption and peripheral arterial disease (PAD) is still insufficiently clearly defined. Moderate alcohol consumption appears to reduce the risk of PAD in seemingly healthy men (1,2). The research conducted by Athyros et al. (3) indicates that moderate alcohol consumption is associated with a lower prevalence of PAD, metabolic syndrome, diabetes, coronary disease, but not with stroke compared to the abstinence from alcohol consumption in the population. Heavy alcohol consumption is associated with an increased prevalence of all abovementioned diseases.

Most preceding epidemiological studies indicate that the risk of PAD is lower in light to moderate alcohol consumers than in abstainers. However, the studies report that heavy consumption is positively associated with the risk of PAD and stroke (4,5). The research conducted by Garcia-Diaz et al. (6) indicates that in patients with PAD, moderate alcohol consumption is associated with lower cardiovascular mortality and total mortality, compared to abstinence. The research conducted by Jepson et al. (7) indicates that the type of alcoholic drink affects the pathogenesis of PAD emphasizing the positive effect of wine, but not of beer and spirits. Vliegenthart et al. (8) indicate a positive effect of moderate alcohol consumption in the pathogenesis of PAD in women and men who do not consume cigarettes.

In the observed Native American population, multivariable analysis (9) results showed a protective effect of alcohol, whereas in the elderly Japanese American male population, the results indicated that alcohol consumption increased rather than decreased the risk of PAD incidents (10). In the observed Chinese population, low alcohol intake was associated with a reduced prevalence of PAD in men, but not in women (11).

The negative effects of alcohol in the pathogenesis of PAD are reflected in a positive correlation with an increase in body weight, total cholesterol level and hypertension (4). The research conducted by Sotoda et al. (12) reveals that in patients with PAD regular alcohol consumption is linked to an increase in HDL cholesterol and a reduction in blood coagulability. Additionally, the progression of atherosclerosis does not differ between non-drinkers and drinkers. The positive effect of moderate alcohol consumption on the pathogenesis of PAD is associated with an increase in HDL cholesterol and blood fibrinolytic activity, as well as with the sensitivity to the effect of insulin and a decrease in LDL cholesterol, inhibition of platelet aggregation and blood coagulability (4).

So far, there has not been a single study regarding the correlation between alcohol consumption and the effect of drug therapy in patients with PAD. Drug therapy of peripheral arterial disease of the lower extremities is very complex, and the goal is to increase the distance covered by patients with intermittent claudication (13,14).

Therefore, the goal of this prospective study is to determine the influence of the correlation between alcohol consumption and the effectiveness of drug therapy in patients with functional ischemia of the lower extremities (FIDE).

## **Patients and research methods**

### ***Study Population***

The study included 82 patients diagnosed with PAD, of which 48.78% of the subjects used pentoxifylline+ASA, while 51.22% of the subjects were treated with cilostazol+ASA.

This prospective clinical study included patients diagnosed with PAD who received outpatient treatment at the Clinic for Vascular Surgery, Clinical Center Niš, between January and December 2020.

Eligible participants were those newly diagnosed with PAD at stage IIa or IIb according to the Fontaine classification (15). Diagnosis was established based on patient history, physical examination, Doppler ultrasonography, and/or multislice computed tomography (MSCT) angiography of the lower extremity arteries.

Exclusion criteria included patients with PAD stages I, III or IV, those with lower limb amputations, left ventricular ejection fraction  $\leq 40\%$ , patients undergoing peritoneal dialysis or hemodialysis, individuals with malignancies and those with comorbidities that could significantly impair general health or physical function.

### ***Methodology***

The study was conducted in accordance with the Declaration of Ethical Principles and the guidelines of Good Clinical Practice (GCP). All participants were fully informed about the study objectives and provided written informed consent prior to enrollment. The research was designed as a prospective cross-sectional study utilizing a structured questionnaire.

### **Assessment of Claudication Distance**

To ensure consistency and accuracy in measurement, patients received detailed instructions on how to assess claudication distance. They were advised to walk at a steady pace and frequency to allow objective evaluation of step count and walking speed. Claudication distance (CD), expressed in meters, was determined using a predefined protocol (16,17). Measurements of CD were recorded at baseline and during follow-up visits at three and six months after the initiation of pharmacological therapy. The differences in claudication distance over time were used to calculate the prolongation of claudication distance (PCD), reflecting changes in walking capacity.

### **Patients group**

Respondents were grouped based on therapeutic modalities and alcohol use:

Based on the applied drug therapy:

- The first group consisted of patients prescribed 400 mg of pentoxifylline three times daily and 100 mg of acetylsalicylic acid (ASA) once daily;
- The second group comprised patients who were prescribed cilostazol at a dosage of 100 mg twice daily, in conjunction with ASA 100 mg of ASA administered once daily.;

Based on the presence/absence of alcohol consumption and the amount of alcohol:

- the first group consisted of patients who consume  $\leq 5$  alcoholic drinks/week
- the second group consisted of patients who consume  $>5$  alcoholic drinks/week.

### **Statistical data processing**

Statistical analysis was conducted utilizing the SPSS 16.0 software package for Windows. The analytical methods employed included both descriptive and inferential statistics. Continuous variables were presented as mean values ( $\bar{X}$ ) accompanied by standard deviations (SD), while categorical variables were expressed as proportions (percentages).

The assessment of the normality of distribution was performed using the Kolmogorov-Smirnov test, whereas the evaluation of the homogeneity of variances was conducted through the Levene test. Parametric methods were applied to evaluate the significance of differences among continuous variables that exhibited a normal distribution. The T-test for independent samples was employed for the comparison of two groups, and one-way ANOVA was utilized for comparisons involving three or more groups. In instances where a statistically significant difference was identified, Tukey's Honestly Significant Difference (HSD) test was applied. A difference was deemed significant at a p-value of less than 0.05.

## **Results**

The values of CD in relation to the choice and duration of medicament therapy are shown in Table 1.

Table1. Values of CD in relation to the choice and duration of medicament therapy (m)

|                   | Cilostazol+ASA |           |        | Pentoxifilline+ASA |           |        |
|-------------------|----------------|-----------|--------|--------------------|-----------|--------|
|                   | N              | $\bar{X}$ | SD     | N                  | $\bar{X}$ | 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 |

\*p< 0,05

The analysis of the therapeutic modalities revealed no statistically significant difference in CD values three months after the therapy was introduced ( $F(1,79) = 0.82$ ;  $p = 0.37$ ; partial eta squared = 0.1). However, the CD analysis conducted six months after therapy initiation showed a statistically significant difference between the medicament therapies ( $F(1, 79) = 5.06$ ;  $p = 0.027$ ; partial eta squared = 0.6). Specifically, the increase in claudication distance was more pronounced in the group of patients who received cilostazol and ASA.

The influence of alcohol consumption and applied therapy on the prolongation of claudication distance is shown in Table 2.

Table 2. Influence of alcohol consumption and applied therapy on the prolongation of claudication distance

|                            | ASA+pentoxifilline |           |        | ASA+ cilostazol |           |        |
|----------------------------|--------------------|-----------|--------|-----------------|-----------|--------|
|                            | N                  | $\bar{X}$ | SD     | N               | $\bar{X}$ | SD     |
| <b>Don't drink alcohol</b> |                    |           |        |                 |           |        |
| After 3 months             | 23                 | 38,91     | 53,51  | 19              | 64,47     | 62,56  |
| After 6 months             | 23                 | 98,04*    | 84,78  | 19              | 167,63*   | 123,66 |
| <b>Drink alcohol</b>       |                    |           |        |                 |           |        |
| After 3 months             | 17                 | 62,06     | 76,10  | 23              | 60,22     | 77,38  |
| After 6 months             | 17                 | 125,88    | 159,64 | 23              | 162,61    | 126,24 |

\*p<0.05

In the cohort of subjects who did not have alcohol consumption, there was no statistically significant change in PCD associated with the administered therapy during the control examination at the 3-month mark ( $t(40) = 1.43$ ,  $p = 0.16$ ; mean difference (MD) = -25.56; 95% confidence interval (CI): -61.75 to 10.63;  $\eta^2 = 0.05$ ). However, at the follow-up examination conducted after 6 months, a statistically significant difference in PCD was identified between the groups under investigation ( $t(40) = 2.16$ ,  $p = 0.04$ ; MD = -69.59; 95% CI: -134.81 to -4.37;  $\eta^2 = 0.10$ ). It is noteworthy that enhanced efficacy was observed in the group treated with cilostazol combined with aspirin (ASA).

Conversely, among the subjects who consumed alcohol, the analysis revealed no statistically significant difference in PCD relative to the therapy administered during the control examination at 3 months ( $t(38) = 0.07$ ,  $p = 0.94$ ; MD = 1.84; 95% CI: -47.91 to 51.60;  $\eta^2 < 0.01$ ). Additionally, no statistically significant differences were detected at the 6-month follow-up after the initiation of therapy ( $t(38) = 0.81$ ,  $p = 0.42$ ; MD = -36.73; 95% CI: -128.20 to -54.74;  $\eta^2 = 0.02$ ).

The influence of alcohol consumption and the therapeutic regimen on the enhancement of claudication distance is presented in Table 3.

Table 3. Influence of the amount of alcohol consumed and the applied therapy on the prolongation of claudication distance

|                                                          | ASA+pentoxifilline |           |        | ASA+ cilostazol |           |        |
|----------------------------------------------------------|--------------------|-----------|--------|-----------------|-----------|--------|
|                                                          | N                  | $\bar{X}$ | SD     | N               | $\bar{X}$ | SD     |
| <b>Consume <math>\leq 5</math> alcoholic drinks/week</b> |                    |           |        |                 |           |        |
| After 3 months                                           | 8                  | 78,75     | 84,97  | 17              | 69,12     | 85,43  |
| After 6 months                                           | 8                  | 156,88    | 183,22 | 17              | 178,53    | 141,58 |
| <b>Consume <math>&gt;5</math> alcoholic drinks/week</b>  |                    |           |        |                 |           |        |
| After 3 months                                           | 9                  | 47,22     | 68,83  | 6               | 35,00     | 44,27  |
| After 6 months                                           | 9                  | 98,33     | 140,65 | 6               | 117,50    | 51,65  |

In the cohort of respondents who consume five or fewer alcoholic drinks per week, no statistically significant change in primary care data (PCD) was observed in relation to the administered therapy. At the three-month follow-up, the statistical analysis yielded the following results:  $t(23) = 0.26$ ,  $p = 0.79$ ; MD = 9.63; 95% confidence interval (CI): -66.01 to 85.28;  $\eta^2 < 0.01$ . Likewise, no statistical significance was noted at the six-month follow-up, with findings indicating  $t(23) = 0.32$ ,  $p = 0.75$ ; MD = -21.65; 95% CI: -159.52 to 116.21;  $\eta^2 < 0.01$ .

In the analysis of subjects consuming more than five alcoholic drinks per week, the three-month follow-up examination similarly revealed no statistically significant change in PCD regarding the applied therapy, with results showing  $t(13) = 0.38$ ,  $p = 0.71$ ; MD = 12.22; 95% CI: -56.75 to 81.20;  $\eta^2 = 0.01$ . Additionally, at the six-month follow-up, no statistical significance was

observed in PCD between the groups analyzed, with findings indicating  $t(13) = 0.32$ ,  $p = 0.76$ ; MD = -19.17; 95% CI: -149.98 to 111.65;  $\eta^2 < 0.01$ .

## Discussion

Drug therapy used in the prophylaxis, reduction of risk factors and therapy of PAD is very complex and requires the application of numerous therapeutic protocols. Antiplatelet drugs (acetylsalicylic acid, clopidogrel and ticlopidine), statins, 5-HT<sub>2A</sub> receptor antagonists, propionyl-L-carnitine carnitines, HMG-CoA reductase inhibitors and antihypertensives (18) are used in all of these protocols. The statistical results of the conducted research indicate a significantly more potent effect of cilostazol compared to pentoxifylline after 6 months of use in general ( $p < 0.05$ ), as well as in the group of patients who do not consume alcohol ( $p < 0.05$ ). In the therapy of intermittent claudication, cilostazol is the most important and it achieves its effect by peripheral vasodilatation, increasing vascular endothelial growth factor, inhibiting platelet aggregation and inhibiting the proliferation of smooth muscle cells (19). There are numerous literature data indicating greater efficacy of cilostazol compared to pentoxifylline in patients with PAD (20-23).

In the group of subjects who consume alcohol, there was no statistically significant difference in PCD compared to the applied therapy at follow-up examinations after 3 and 6 months. Additionally, concerning the applied therapeutic modalities, there was no statistically significant PCD in the group of subjects related to the consumption habits of the number of alcoholic drinks per day at the follow-up examinations after 3 and 6 months. The conducted research is the first research regarding the correlation between the effect of alcohol consumption

and the forementioned therapeutic modalities in patients with PAD, which makes the comparison with the results of other researches difficult.

The research results indicate that in the group of patients who consume alcohol, the dominant effect of cilostazol vanishes compared to pentoxifylline. The reasons for this should be pursued in the analysis of alcohol, pentoxifylline and cilostazol metabolism. Alcohol is metabolized mainly in the liver where it is converted into acetaldehyde. Two systems contribute to this metabolism, predominantly the alcohol dehydrogenase pathway and cytochrome P450 (P450) 2E1, as well as the pathway controlled by the microsomal ethanol oxidation system (MEOS), which is inducible and also involved in the metabolism of other drugs (24). P450 are a superfamily of enzymes involved in the metabolism of various compounds in the body, including alcohol. They are membrane-bound hemoproteins that play a key role in xenobiotic detoxification, cellular metabolism, and homeostasis. Induction or inhibition of cytochrome enzymes is the main mechanism underlying drug-drug interactions (25). The metabolism of pentoxifylline in the liver predominantly occurs via P450 1A2 (26), while the metabolism of cilostazol occurs via P450 3A4, P 450 3A5, P450 2C19 (27-28). The P450 2E1 is a key enzyme of the microsomal pathway of ethanol oxidation. In patients with chronic alcohol consumption, its activity increases three to five times in the liver of alcoholics. This induction affects P450 3A4 and 1A2, which contributes to the metabolic tolerance of alcohol and drugs that are metabolized by this pathway such as cilostazol (27). The expected significant effect on therapeutic modalities in the group of patients consuming more alcoholic drinks per week was absent. The explanation, and at the same time the weakness of the study, can be found in the fact that the type of consumed alcoholic drink was not analyzed, given that the conducted research indicated the importance of this parameter (7).

The obtained research results indicate that patients with PAD who use cilostazol should be counseled to stop consuming alcoholic drinks because they reduce the therapeutic effect, regardless of several literature data indicating the beneficial effects of low or moderate alcohol consumption in patients with PAD (2-4, 6-9,11).

### **Conclusion**

Statistical results indicate that significantly more favorable effect of cilostazol compared to pentoxifylline, verified in general, as well as in the group of patients who did not consume alcohol, was absent in the group of patients who consumed alcohol. The number of alcoholic drinks that the patient consumed per week did not have a statistically significant influence on the effectiveness of the applied therapeutic modalities in patients with PAD.

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### **Conflict of interest**

The authors declare no conflict of interest.

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