GSC Biological and Pharmaceutical Sciences

eISSN: 2581-3250 CODEN (USA): GBPSC2

Cross Ref DOI: 10.30574/gscbps

Journal homepage: https://gsconlinepress.com/journals/gscbps/

(REVIEW ARTICLE)

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Contemporary view on chronic limb ischemia

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GSC Biological and Pharmaceutical Sciences, 2022, 21(01), 020–025

Publication history: Received on 22 August 2022, revised on 27 September 2022, accepted on 30 September 2022

Article DOI: https://doi.org/10.30574/gscbps.2022.21.1.0373

Abstract

Chronic limb ischemia is a progressive and life threatening disease which in turn effects on quality of life. Up to date several studies have been conducted to timely identify and manage of the disease. Timely identification, diagnosis and treatment of this pathological condition will play crucial role to reduce burden in healthcare associated with this disorder. In this article latest data are shown on chronic limb ischemia, its pathophysiology, and treatment and prevention measurements together with general information on this disorder. Furthermore, latest clinical trials and studies are summarized in order in depth understand the exact mechanisms of the disease.

Keywords: Chronic limb ischemia; Peripheral artery disease of the lower extremities; Atherosclerosis

1. Introduction

Chronic obliterating diseases of the arteries of the lower extremities (COLA) is one of the most common cardiovascular diseases in the population. The prevalence of intermittent claudication (IC) varies with age from 0.9 to 7.0% with an increase in older age groups: 1-5% in people under 50 years of age, 10-14% in people aged 50-70 years [1]. Surgical methods for the treatment of COLA continue to develop rapidly, and the proportion of X-ray endovascular interventions is constantly growing. In Uzbekistan, due to insufficient provision of the population with specialized angiosurgical care, only a small proportion of patients with chronic lower limb ischemia (CLLI) receive it. Most of these patients are patients of general, and primarily outpatient, surgeons. The primary appeal for medical care occurs when the clinic of IC appears, which corresponds to the IIA-IIB degree of ischemia according to the Pokrovsky-Fontein classification and reduces the quality of life of patients.

It should also be noted the high incidence, 45-65 cases per 100 thousand population [2] of the development of critical lower limb ischemia (CLLI). The reason for this is the insufficiently high efficiency of the ongoing conservative therapy and prevention of the progression of chronic arterial insufficiency. As a result, major limb amputation is performed in 25–30% of cases within 1 year after the diagnosis of CLLI is established [3]. Within 5 years after primary amputation, death occurs in 70% of cases [4].

Taking into account these data, the need to improve the conservative element of treatment of patients with CLCI should be recognized. In particular, the introduction of modern methods of treatment, the development of prevention of the progression of the underlying disease in the practice of an outpatient surgeon are required.

The basis of conservative treatment of peripheral arterial diseases are measures aimed at correcting risk factors (smoking, arterial hypertension (AH), diabetes mellitus, hyperlipidemia, hyperhomocysteinemia), and therapeutic physical culture (exercise therapy). According to the 2017 ESC Guidelines on the Diagnosis and treatment of Peripheral Arterial Diseases, In Collaboration with the European Society for Vascular Surgery (ESVS), the mainstay of treatment

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for intermittent claudication (IC) should be smoking cessation in conjunction with daily exercise therapy (the best effect is shown by dosed walking) [6].

Up to 80% of patients with CLCI are smokers [7]. Quitting smoking can help prevent the progression of the disease. Smoking after bypass surgery increases the risk of postoperative shunt thrombosis by at least 3 times [8].

In addition to smoking, an important role is played by the level of cholesterol in the patient's blood. All patients with peripheral arterial disease should receive statins, regardless of blood lipoprotein levels. This conclusion is based on the Heart Protection Study (20,536 patients, 6,748 of them with COZANK), which showed that the risk of coronary circulation disorders in the group taking statins (simvastatin 40 mg) is reduced by 22% compared with the placebo group [4]. Statins should definitely be included in the treatment of CP (level of evidence IA). In addition to the fact that lipid-lowering therapy significantly reduces the risk of developing cardiac complications, several meta-analyses have shown a positive effect of statin administration on pain-free walking distance (PCD) and maximum walking distance (MPD) [9].

In patients with peripheral arterial disease, hypertension also needs to be corrected. Target BP values are 140/90 mm Hg, and if the patient has diabetes mellitus and chronic kidney disease or is less than 60 years old, 140/85 mm Hg. [5]. Among antihypertensive drugs, preference should be given to blockers, angiotensin II receptors and angiotensin-converting enzyme inhibitors due to the peripheral vasodilating effect of these drugs. β-blockers are not included in the first-line drugs for the treatment of hypertension, they are used to prevent myocardial infarction (MI), atrial fibrillation. One of the most significant risk factors are disorders of carbohydrate metabolism in the body, namely diabetes mellitus. Patients with COLA and diabetes mellitus need reasonable and complex treatment. For many years, the target values of glycated hemoglobin were considered to be 7% or less, but recently, more and more people are inclined to believe that an individual approach to each patient is necessary [10].

Obesity plays an important role in the progression of ischemia. It has been noted that in patients with COLA, normalization of body weight can potentially increase CLCI [11].

Exercise therapy is one of the most effective treatments for P.H. According to the ESVS, dosed exercise therapy should be recommended for patients with CLCI (level of evidence IA). Studies have been conducted in which exercise therapy has been compared with other forms of treatment. When compared with antiplatelet therapy, the maximum passable time in the exercise therapy group after 6 months increased by 86%, while in the group receiving antiplatelet drugs only by 38%. Differences in the parameters of the ankle-brachial index (ABI) and peak blood flow of the lower leg were not found [12].

2. Medical treatment

The basis of conservative therapy for cardiovascular diseases in general and peripheral arterial diseases in particular is the use of antiplatelet agents. Aspirin has been shown to significantly reduce the risk of MI, stroke, or death (level of evidence IA) (Antithrombotic Trialists' Collaboration, n=135,000). In the group of patients with COLA, taking aspirin at various dosages reduced the risk of the above events by 22%. According to the ESVS, patients with symptomatic peripheral arterial disease should receive antiplatelet agents (clopidogrel or aspirin) for a long time (level of evidence IA) [1]. So far, it is impossible to talk about the advantage of dual antiplatelet therapy over aspirin monotherapy as a prevention of the development of cardiovascular complications in patients with CLCI due to lack of information [12]. In the group of patients receiving dual antiplatelet therapy, there was a decrease in the incidence of MI compared with the group of patients who received only aspirin, but an increase in the number of "major", including fatal, bleeding was also noted.

After interventions on the vessels of the lower extremities, patients are recommended to take aspirin (level of evidence IA) [6]. According to some researchers [7], clopidogrel should be used instead of aspirin as an antiplatelet agent in the treatment of patients with CILC, in particular in cases of intolerance to acetylsalicylic acid (level of evidence IIB). According to the results of the ECLID study (n=13,885), which compared the effectiveness of taking clopidogrel and ticagrelor in relation to the development of cardiovascular complications and bleeding, there were no significant differences in the studied groups [13]. Antagonists of GPIIb/IIIa receptors (integrilin is the most commonly used) have not shown significant benefit in patients with atherosclerosis of the arteries of the lower extremities [14].

Pentoxifylline is one of the main drugs that relieve PH. It is a vasodilator drug with an additional antiplatelet effect, mainly affecting the microcirculation. The antiplatelet effect is secondary, so it is possible to prescribe pentoxifylline in combination with other antiplatelet agents, antiplatelet drugs [15]. Petoxifylline is a first-line drug not only in the

Russian Federation, but also in many countries around the world: in the United States, for many years, pentoxifylline was the only FDA-approved drug for the treatment of peripheral arterial disease. A significant number of studies confirm the positive effect of pentoxifylline on DBC and IVD [16].

There have been many studies comparing the effectiveness of various drugs and treatment methods with pentoxifylline therapy: when compared with exercise therapy after 13 weeks, the maximum passage time increased in the pentoxifylline group by 88% versus 62% in the exercise therapy group [17]. Iloprost showed results worse than pentoxifylline [18], and when comparing alprostadil with pentoxifylline, the differences in MTD and DBC were insignificant [19]. When comparing the effectiveness of bufomedil, pentoxifylline, and nifedipine, based on the results of a 90-day study, it was concluded that nifedipine had the best effect in the treatment of CP, followed by pentoxifylline, and the least effect was bifomedil [20]. When taking pentoxifylline, patients developed dyspepsia, headache, pharyngitis, and pain in the extremities. But at the same time, the appearance of the same complaints was also noted in the placebo groups, so it should not be argued that pentoxifylline is directly related to these complications.

In world practice, one of the main drugs for the treatment of IC is cilostazol, a phosphodiesterase-3 inhibitor that has an antiplatelet and antiaggregant effect [20]. In addition, cilostazol has a vasodilating effect, positively affects the concentration of triglycerides and high-density lipids [21]. A contraindication to taking cilostazol in the first place is the presence of chronic heart failure, liver and kidney failure in a patient [21, 22]. The recommended dose of cilostazol for IC is 100 mg twice a day, however, many studies have been conducted with different dosages of the drug. When taking the recommended dose of cilostazol, many studies have shown an undeniable positive effect on the clinical manifestations of CLLI [23]: the average increase in IVD compared with the placebo group was 43.11 m (from 18.27 to 67.9 m). The effect on LPT cannot be considered significant: Dawson (2000) reported a mean increase in ABI in the cilostazol group of 0.04, while the mean ABI fell by 0.01 in the placebo group.

At the same time, there are studies indicating a negative effect of cilostazol: Otsuka Study 21-86-103 showed a decrease in IVD by 6.9 m when taking cilostazol and an increase by 30 m in the placebo group (statistical deviation of the geometric mean was 0.83 in favor of placebo). Otsuka Study also showed negative results. In contrast, Strandness (2002) et al. compared cilostazol 50 mg with placebo and showed a pronounced positive effect (an increase in DBC in the cilostazol group by an average of 32 m compared with the placebo group) [23]. Taking cilostazol at a dose of 150 mg 2 times a day also has a positive effect (MTD in the cilostazol group increased by 51.8 m compared with the placebo group) [21].

When comparing cilostazol and pentoxifylline, ambiguous results were obtained: in some, cilostazol was preferred [24], in others, no difference was found between the effectiveness of the drugs [25]. Among the side effects when taking cilostazol, the most common were headache, diarrhea, stool disorders, dizziness, tachycardia, and pain in the limb. Convincing data on the effect of cilostazol on mortality have not been obtained. Promising results are shown by the use of naftidrofuryl. This drug blocks 5-HT2 receptors, thereby improving blood circulation in the ischemic zone and increasing ATP production. In addition, its vasodilation effect should be noted. At the moment, this drug occupies 52% of the UK market.

In studies [26], data were obtained on a significant positive effect of naftidrofuril: DBC and MTD compared with their values in the placebo group increased by 49 and 60%, respectively. Naftidrofuril showed better results compared to cilostazol and pentoxifylline in assessing DBC and IVD [27].

Prostacyclin analogues (eg, iloprost, prostaglandin I2) are also used to treat CINC. Iloprost has an antiplatelet property, in addition, it activates fibrinolysis, inhibits adhesion and activation of platelets, as well as adhesion and migration of leukocytes after endothelial damage. The vasodilating effect of the drug is manifested at the level of venules and arterioles. Despite the fact that prostaglandins are most often used to treat critical ischemia, there are studies on the effect of the drug on HRP: 6 months after the start of the study, an increase in MTD by 7.7, 8.8 and 11.2% was noted when taking 50, 100 and 11.2%, respectively. 150 ng twice a day compared to baseline. Interestingly, in the placebo group, an increase in MTD of 3.3% compared with baseline values was noted. Among the side effects of iloprost, headache was most often noted (44-67% depending on the dosage), there were also cases of diarrhea, pain in the limb, dilation of subcutaneous vessels [16]. In addition to I2 prostaglandins, E1 prostaglandins are used to treat CINC. Basically, this group of drugs finds its application in the treatment of CLLI.

It is believed that the use of dietary supplements (in particular, propionyl-L-carnitine) can have a positive effect as a component of cardiovascular disease therapy. The main effect is antioxidant. Propionyl-L-carnitine is responsible for transporting fatty acids across the mitochondrial membrane. In [12], the effect of this dietary supplement on peripheral arterial diseases was shown. The study evaluated the indicators of the maximum walking time, as well as the time of

pain-free walking. There were no data on significant differences in the change in the studied parameters between the treatment and placebo groups, as well as on serious complications associated with taking the drug.

Actovegin is a biological drug used in the treatment of atherosclerosis. The drug is a combination of more than 200 bioactive molecules [28], which was shown using gas and liquid chromography. One of the most important features of Actovegin is its insulin-like action, which confirms the significant positive effect of the drug in patients with type 2 diabetes mellitus [29]. Actovegin protects liver cells, myocardium, neurons from hypoxia, which helps to improve metabolism at the cell level in ischemic tissue damage, in addition, the drug reduces the rate of apoptosis [30]. In case of circulatory disorders in the lower extremities, actovegin has a stimulating effect on wound healing [31]. Actovegin has a positive effect on the microcirculation of ischemic tissues of the lower extremities and increases their oxygenation, which stimulates reparative processes in the affected extremities [32].

Sulodexide (belongs to the group of heparinoids) reduces platelet aggregation and adhesion, and is also involved in the stimulation of fibrinolysis due to increased release of plasminogen activators from the endothelium. Studies confirm the positive effect of sulodexide on the clinic of CP: DHH increased by 95%, MDC - by 70%, the level of fibrinogen decreased by 15%. At the same time, no serious complications associated with taking the drug were noted [17]. Genetic therapy as a method of stimulating angiogenesis can be considered a promising direction in the development of CINC therapy. Currently, several growth factors are used for treatment: endothelium, placenta, fibroblasts, hepatocytes, etc.

There are several ways to administer factors: intramuscular, intraarterial, and subcutaneous [32].

Some gene therapy studies have used the likelihood of limb amputation compared with standard treatment to assess the effect of treatment. A positive effect of the treatment on this indicator was noted (14% versus 30%) [12]. There were no significant differences between the control and study groups in terms of the probability of a lethal outcome - 12 and 14%, respectively, within 1 year, 9 and 12% - within 2 years. The incidence of serious complications in the groups was also approximately the same.

In other studies [33], the effectiveness of gene therapy was assessed by subjective criteria (HBH, IVD, pain-free walking time, maximum walking time). If Deev (2015) indicates an increase in HBC in the study group compared to the control group (by 151, 231, and 251 m after 6, 12, and 24 months, respectively), then a meta-analysis of the conducted studies did not reveal significant differences between the groups.

Deev (2015) et al. assessed ABI in patients treated with growth factors [33]. There was only a slight increase in ABI in the study group compared with the placebo group (+0.04) [34].

The only gene therapy drug allowed in the Russian Federation is Neovasculgen, the active substance is a plasmid with the gene for endothelial growth factor (VEGF165). The mechanism of action is stimulation of the growth of collateral vessels, microvasculature in ischemic tissues. The indication for the use of neovasculgen is CINC II-III degree according to the Fontaine-Pokrovsky classification. The drug is recommended to be administered intramuscularly into the lower or middle third of the gastrocnemius muscle along its posterior surface [35]. There are studies that have shown that the use of neovasculgen has a stable positive effect in the form of an increase in HBC in most patients [46], in particular, in the long-term period - at least 5 years [36].

Thus, different drugs affect different stages of the pathogenesis of P.H. However, there is no reason to talk about the exclusive advantage of any of the drugs, since the results vary significantly depending on the studies and the accumulated information is still insufficient [37].

3. Conclusion

Based on the data of the world literature, there are many drugs whose action is aimed at the treatment of PH corresponding to the IIA-IIB degree of ischemia according to the Fontaine-Pokrovsky classification. The issue of adjusting risk factors can no longer be considered so acute: the evidence-based results of the conducted studies have made it possible to develop national recommendations and guidelines in which the directions for such adjustment are quite clearly defined. If we talk about the direct treatment of PC, then convincing data on efficacy that would meet the criteria of evidence-based medicine have been obtained to date only for drugs from the group of antiplatelet agents. But even there, studies of the comparative efficacy of various drugs and treatment regimens are still ongoing, therefore, the need for further study is obvious, which will allow optimizing the conservative, namely, medical, treatment of patients with CLCI, in particular in the practice of an outpatient surgeon.

Compliance with ethical standards

Acknowledgments

Authors thank to the TMA for technical support.

Disclosure of conflict of interest

No conflict of interest.

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