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(REVIEW ARTICLE)

Treatment of critical ischemia of the lower extremities

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Abstract

Chronic ischemia of the lower extremities (CLLI) remains one of the main socio-economic problems modern medicine. The problem of treating patients with intermittent claudication, despite the rapid development of medical technologies, remains one of the most significant in medicine. The progression of the disease leads to the development of complications such as major cardiovascular events, the development of critical lower limb ischemia (CLLI), as well as amputations, which are disabling diseases. In this article broad notion are summarized on critical limb ischemia, scope of the problem, its treatment and modern approaches for the management of this disorder. Besides, latest clinical trials and study results are stated in order in depth understand the management of the disease.

Keywords: Atherosclerosis; Dyslipidemia; Peripheral artery disease; Critical lower limb ischemia; Diabetes mellitus.

1. Introduction

Atherosclerotic peripheral arterial disease (PAD) is an atheromatous lesion that results in occlusion or stenosis of the vessels of the lower extremities. PAD may present with varying degrees of symptoms or be asymptomatic. To determine the degree of this disease, the Fontan classification in Europe and the Rutherfod classification in North America are used. The extreme degree of manifestation of the disease is critical lower limb ischemia (CLLI), in which the arterial blood supply does not provide the metabolic needs of the limb even at rest. The main features of PAD are resting limb pain, ischemic ulcers, and ischemic gangrene of the dorsum of the foot or toes. Atrophy, pallor and scalyness of the skin can also be observed due to a violation of the trophism of the subcutaneous tissue, intermittent hyperemia, loss of hairline and thickening of the nail plate. Chronic diseases of the arteries of the lower extremities (CDALE) are severe pathological conditions, the result of the manifestations of which can be a patient's disability and even death. The clinical manifestation of damage to the arteries of the lower extremities is very diverse, ranging from an asymptomatic course to critical ischemia and gangrene of the lower extremity. The term "critical lower limb ischemia" was first introduced by P.R. Bell in 1982. Manifestations of critical ischemia are pain at rest, as well as the presence of necrotic changes in the fingers or foot, caused by a decrease in distal tissue perfusion below the level of metabolic needs of the resting state [1]. This pathological condition occurs in 50 to 100 cases for every 100,000 people in the US and European countries [2]. The main pathological factor leading to this condition is stenosis and occlusion of the arterial bed due to various pathological conditions, the main of which is atherosclerosis of the vessels of the lower extremities. Risk factors for the development of atherosclerosis, and thus CDALE, are other common pathological conditions such as arterial hypertension, diabetes mellitus, hypercholesterolemia, and smoking. In modern medicine, there is a wide arsenal of methods for the treatment of critical lower limb ischemia, ranging from conservative therapy with the use of vasotropic drugs and substances that improve blood rheology, up to X-ray endovascular treatments and, more recently, gene therapy. Currently, a huge number of studies have been conducted, the results of which confirm the effectiveness of conservative therapy in patients with critical ischemia of the lower extremities. In one study, authors analyzed the effectiveness of prostaglandin E1 in patients with critical ischemia of the lower extremities on the background of

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diabetes mellitus - this is one of the severe groups of patients with critical ischemia. Against the background of the treatment, the patients showed an increase in the ankle-brachial index (ABI), linear blood flow velocity and pulse index. As for the subjective aspects, 75% of patients noted a significant improvement in their condition, but 20% noted that there were no significant changes, 5% complained of a deterioration in their condition. Thus, it was concluded that prostaglandin E1 can be used in the treatment of critical lower limb ischemia, especially in patients who cannot undergo revascularization surgery [2]. One of the main methods of treatment of critical ischemia is reconstructive surgery on the arteries of the lower extremities. Currently, there are treatment algorithms, as well as principles for the use of surgical correction methods, both with the use of artificial conduits and with the use of venous autoconduits. In one study authors provide data on the performance of 122 bypass operations using a venous conduit, where the distal anastomosis was placed on one of the arteries of the foot. Patency during 3 years, 5 years was 58.2% and 53.4, respectively. Limb preservation was achieved in 70% within 3 years and in 50.4% within 5 years [3]. However, there was a huge group of patients who did not have the opportunity to perform a reconstructive operation, who had damage to several vascular beds, which made the risk of surgery high, or they had a pronounced lesion of the distal bed.

The development of X-ray endovascular surgery in the second half of the twentieth century gave vascular surgeons a new method of treating critical ischemia. According to a recent study, the survival rate of the limb during the year after the use of X-ray endovascular technique in the treatment of critical ischemia was 93.5%. Technical success was initially achieved in 84% of cases [4]. In another anological study by compared the results of treatment of patients with critical ischemia who underwent open surgery and patients who were treated using X-ray endovascular techniques. Technical success was achieved in 90% of cases in both groups, however, the rate of complications and the number of major amputations were significantly higher in the group of patients with surgical revascularization. At 1, 3, 5 years, the limb preservation and survival rates were 94.4, 72.7, and 52.2% in the open surgery group, and 89.7, 67.2, and 46.3% in the X-ray endovascular technique group [5]. Japanese authors also pointed out that the incidence of postoperative complications is higher in the group of patients who underwent surgical revascularization. However, primary patency over a three-year interval was lower in the endovascular group and was 55% versus 71% in the open surgery group. The limb salvage rate was also lower, 81% versus 85%, respectively [6]. In one study authors evaluated the effectiveness of transluminal balloon angioplasty in patients with critical ischemia with concomitant diabetes mellitus. Technical success was achieved in 90% of cases. In 85% of cases, there was a regression of the symptoms of critical ischemia in the form of healing of trophic ulcers and the disappearance of pain at rest [7]. Also another author demonstrated that the treatment of 126 patients with critical ischemia using X-ray endovascular techniques, including intraluminal angioplasty, subintimal angioplasty and stenting, are presented. Technical success was achieved in 89% of cases, clinical success in 87%. Subintimal angioplasty was used for extended occlusions, more than 10 cm, with a success rate of 79%. [8]. In 2018 Korean authors presented data on patients with critical ischemia and occlusion of the arteries of the lower leg and foot, who underwent subintimal angioplasty (SA). 309 procedures were performed on various arterial segments of the lower leg. Given the complexity of the procedure, the authors note that in 63% of cases arterial perforation occurred, in half of which there was no possibility of using the reentry mechanism. The absence of blood flow after SA was observed only in 6% of cases. Success was achieved in 77% of cases. [9] Authors emphasized the presence of patients with an atypical variant of the blood supply to the foot, when the dorsal artery of the foot or the burned artery of the foot were a continuation of the peroneal artery. As a result, patients had hypoplastic tibial arteries, which led to a high risk of perforation. The frequency of occurrence of such variants was about 7% [10].

2. Associated atherosclerotic diseases and cardiovascular risk

Peripheral artery disease is usually a manifestation of systemic atherosclerosis, so morbidity and mortality are closely correlated with those of myocardial infarction and stroke. About 30–50% of patients with PAD have a history of coronary heart disease (CHD). Significant involvement of at least one coronary artery occurs in 60–80% of patients with peripheral artery disease [11], and hemodynamically significant narrowing of the carotid artery is diagnosed in 12–25% of patients using duplex ultrasound [12]. The atherosclerotic process affecting other vessels explains the increased risk of myocardial infarction, stroke, and cardiovascular mortality in patients with PAD. Annual cardiovascular mortality (due to myocardial infarction, ischemic stroke, vascular events) is 5–7%. In the presence of PAD, the risk of developing myocardial infarction increases by 20–60%, and the risk of death from coronary artery disease increases by 2–6 times [13]. The risk of stroke also increases by 40%. Moreover, the severity of PAD correlates with the frequency of transient ischemic attacks and strokes [14]. Patients with severe PAD and CLLI have a higher risk of developing myocardial infarction and stroke than patients with a moderate form of the disease. Myocardial infarction and stroke are the main causes of death in patients with CLLI. The annual mortality in patients with CLLI is 25%, and in those who have undergone amputation it is 45% [15].

3. Disease progression and condition of the limb

The nature of the course of the disease (symptomatic or asymptomatic) does not reflect the rate of its progression. The presence of symptoms is more determined by the activity of the patient than by the stage of the disease. In some patients, CLLI is diagnosed at the initial examination, because, despite the fact that the degree of their activity was insignificant for the manifestation of symptoms of intermittent claudication, the revealed decrease in perfusion in the limb is significant for the violation of healing of even the slightest damage. Approximately 25% of patients with symptoms of intermittent claudication experience significant progression of the disease and worsening of symptoms within the first year after diagnosis. In the remaining 75% of patients, stabilization of the condition occurs due to the development of collaterals, metabolic adaptation of the affected tissues and the involvement of alternative muscle groups during walking. Atherosclerotic lesion, which underlies CLLI, has a diffuse, multisegmental character. Concomitant factors such as diabetes mellitus (DM) and conditions accompanied by low cardiac output play a significant role in the progression of the disease. Due to these factors, the blood flow in the microvasculature is significantly reduced.

Currently, most of the patients suffering from CLLI receive surgical or endovascular treatment, so it is rather difficult to determine the natural course of the disease. Despite this, there remains a proportion of patients for whom revascularization is not indicated or for whom its attempts were ineffective. Many patients in this category are included in randomized controlled trials (RCTs) to study the effectiveness of pharmacotherapy and to determine the prognosis of the disease without revascularization. Approximately 40% of patients in this group will undergo amputation within 6 months, and 20% will die [16]. As a result of the observation, it was found that within 1 year only 50% of patients will remain alive without massive amputation, 25% of patients will die and 25% will need massive surgery. Thus, the diagnosis of CLLI has a negative prognostic value in terms of patient mortality and limb vital function.

In patients with CLLI, clinical symptoms and complications are due to pathophysiological disorders due to multilevel vascular lesions [17]. As shown in Figure 2, in addition to the state of general hypoperfusion due to arterial stenosis, irrational blood supply to the skin due to macro- and microcirculatory disorders is characteristic. Medical therapy is aimed at restoring microcirculation instead of revascularization and provides treatment for patients who are not indicated for endovascular interventions.

4. Smoking cessation

The relationship between smoking and an increased risk of developing atherosclerosis has long been proven. Indeed, mortality, the risk of limb amputation, peripheral shunt occlusion, and cardiovascular events have a dose-dependent correlation with tobacco smoking [18]. A systematic review of 20 studies showed that smoking cessation was associated with a 36% reduction in the relative risk of mortality compared with the same risk in patients who continued to smoke [relative risk ratio (RR) 0.64; 95% confidence interval (CI) 0.58–0.71] [19]. Less clear is the effect of smoking cessation on limb viability. On this basis, the importance of smoking cessation should be explained to patients in terms of cardiovascular events, disease progression and amputation, and not in terms of symptomatic treatment. There are a large number of proven effective ways to completely quit smoking [20].

5. Hyper lipidaemia

Increased levels of total cholesterol, low-density lipoprotein (LDL), triglycerides, and lipoproteins (a) are independent risk factors for the development of PAD. Conversely, elevated levels of high-density lipoprotein (HDL) and apolipoprotein (a-1) have a protective effect on the vessel wall. According to the TASC II guidelines [21], LDL-C in patients with PAD, regardless of the presence or absence of symptoms, should be less than 2.59 mmol/L. In the presence of a history of vascular disease in other locations (for example, coronary artery disease), the recommended target LDL level is 1.81 mmol / l. In patients with symptoms of PAD, statins are first-line drugs to lower LDL cholesterol and reduce the risk of cardiovascular events. A subgroup study of 6748 PAD patients enrolled in the Heart Protection study found a significant reduction in all-cause mortality, vascular mortality, acute coronary syndromes, stroke, and non-coronary revascularization with simvastatin [22]. The minimum cholesterol threshold below which there would be no positive effect of statins has not been identified. In patients with PAD who have abnormal HDL and cholesterol fractions, fibrates and/or niacin should be considered to correct dyslipidemia.

6. Arterial hypertension

All recommendations for the treatment of arterial hypertension (AH) emphasize the need for strict control of blood pressure (BP) in patients with atherosclerosis, including patients with PAD. In the latest recommendations of the

European Society of Cardiology, the recommended target blood pressure for all patients with hypertension is 140/90 mmHg, and for patients with diabetes or cerebrovascular disease - 130/90 mmHg. Patients with CLLI belong to the high-risk group, so it is recommended for them to achieve a lower target BP value [23]. In patients with CLLI, the goal is to achieve a normotensive state. However, strict control of pressure reduction is necessary to prevent a critical decrease in limb perfusion and disease progression. Periods of a sharp decrease in blood pressure can increase the likelihood of amputation. All antihypertensive drugs reduce the risk of cardiovascular events, mainly by directly lowering blood pressure.

In the Heart Outcomes Prevention Evaluation (HOPE) study, a subgroup of 4,046 patients with PAD demonstrated a 22% risk reduction in patients randomized to the ACE inhibitor ramipril compared with a placebo group not affected by BP reduction. It is possible that ACE inhibitors have a cardioprotective effect independent of their antihypertensive efficacy. Based on the findings, the TASC II team recommends prescribing this group of drugs to patients with PAD.

In the past, the use of β-adrenergic blockers (β-blockers) in PAD was limited due to the possible progression of symptoms during this therapy. However, this fear was not confirmed in RCTs, so b-blockers can be freely prescribed for intermittent claudication [24]. The appointment of b-blockers is especially necessary in patients with concomitant coronary artery disease, since this group of drugs has a cardioprotective effect.

7. Diabetes

Active control of blood glucose levels in type 1 and type 2 DM reduces the incidence of microvascular complications (retinopathy and nephropathy), but the effectiveness of glycemic control in patients with PAD is not so obvious. The main reason for this is the lack of glycemic profile studies in patients with DM and PAD. Further research is needed to investigate the effect of glycemic control on the course of PAD. However, maintenance of normal glycemic levels is recommended, as this reduces the incidence of cardiovascular events in high-risk patients.

8. Antiplatelet therapy

The Antithrombotic Trialists' Collaboration conducted a meta-analysis of clinical trials of antiplatelet therapy in high-risk patients with vascular disease [25]. Among patients with PAD treated with antiplatelet drugs (9716 patients in 42 studies), there was a proportional reduction in the incidence of cardiovascular events such as myocardial infarction, stroke and vascular mortality by 23%. Similar beneficial effects have been seen in patients with intermittent claudication who have undergone peripheral artery bypass surgery or angioplasty. Most of the studies in patients with PAD have used ticlopidine, while the rest have investigated the effects of aspirin, picotamide, dipyridamole, and clopidogrel. The findings of a systematic review [26] support the findings of the Antiplatelet Research Working Group. It should be noted that the use of ticlopidine is limited, since the drug causes neutropenia and thrombocytopenia. In addition to reducing the risk of myocardial infarction, stroke, and vascular death, antiplatelet drugs also reduce the risk of arterial occlusion in patients with PAD. Based on a meta-analysis of 54 RCTs in patients with intermittent claudication, aspirin was shown to reduce the risk of arterial occlusion compared with placebo, and ticlopidine reduced the need for revascularization [38].

The recommended dose of aspirin is 75–150 mg [27] or 75–325 mg [28]. As an alternative to aspirin for the prevention of cardiovascular events, clopidogrel can be prescribed [29]. In the study "Clopidogrel for High Atherothrombotic Risk and Ischemic Stabilization, Management, and Avoidance (CHARISMA)", when analyzing a subgroup of patients taking clopidogrel, of which only a quarter suffered from PAD, it was found that dual antiplatelet therapy with clopidogrel and aspirin had a slight advantage over therapy only aspirin and was associated with an increased risk of bleeding [30]. Thus, there are no convincing data in favor of dual antiplatelet therapy, therefore its administration is not recommended in patients with PAD [31].

9. Anticoagulant therapy

Experience with the use of warfarin in patients with atherosclerosis is based on the results of studies in patients with coronary artery disease. Two meta-analyses demonstrated that warfarin at medium and high doses reduces mortality, the risk of heart attack and stroke, but at the same time increases the incidence of bleeding [32]. When comparing the effectiveness of warfarin (with the achievement of a target INR of 3.0-4.5) and aspirin (at a dose of 80 mg) in patients undergoing infrainguinal bypass surgery for obliterating peripheral artery disease, the number of postoperative shunt occlusions was similar in the two groups [33]. The risk of bleeding in patients taking anticoagulants was almost twice

as high. Thus, there is currently insufficient evidence to recommend anticoagulant therapy for the prevention of vascular complications or arterial occlusion in patients with obliterating diseases of the lower extremities.

A Cochrane systematic review reviewed the use of heparin in the treatment of intermittent claudication [34]. There was no statistically significant difference in the number of cardiovascular events in the appointment of heparin compared with placebo. There are no data on the positive or negative effect of subcutaneous heparin in combination with aspirin on the length of the distance traveled [35]. Thus, heparin is not recommended for patients with intermittent claudication.

10. Homocysteine

Elevated homocysteine levels are an independent risk factor for atherosclerosis. Its level can be reduced with the help of B vitamins and folic acid, but the effect of lowering homocysteine levels on the course of obliterating peripheral artery disease has not been studied. Two studies looking at the addition of B vitamins and folic acid to patients with CAD found no benefit and suggested harm [36,37]. Thus, actively lowering homocysteine levels in patients with PAD is not recommended.

11. Use of drug-eluting stents

The use of drug-eluting stents to prevent the development of neointimal hyperplasia is the standard in coronary angioplasty. Recent studies have examined the benefit of these stents in PAD. Sirolimus, everolimus, and paclitaxel are used as coatings for stents and balloons. Coated stents and balloons are believed to be safe and may be effective in preventing restenosis [38]. As research is completed and evidence accumulates regarding the use of stents and coated balloons, it may be concluded that they are effective in preventing the incidence of restenosis.

12. Thrombolysis

With a sharp decrease in limb perfusion, acute ischemia occurs, which poses a threat to the viability of the limb. In most cases, the cause of ischemia is thrombosis of the affected vessel, or thromboembolism. In more rare cases, graft occlusion, trauma or thrombosis of a peripheral aneurysm is diagnosed [39]. In patients with thromboembolism, aneurysmal sac thrombosis, or shunt occlusion, clinical manifestations of ischemia occur within hours, and in patients with chronic thrombosis, they may be delayed. Shunt thrombosis is also possible. The goal of emergency therapy is to prevent the progression of thrombosis and aggravation of ischemia, for this, anticoagulant therapy with heparin is used. Recanalization of the artery and restoration of perfusion can be carried out in several ways: surgically, with the introduction of thrombolytics, or using various endovascular techniques for removing a thrombus. This section focuses on thrombolysis. A recent Cochrane review comparing the efficacy of surgery and thrombolysis in acute limb ischemia found no significant difference in the incidence of limb survival or limb necrosis at 30 days, 6 months, or 1 year after care. Patients who underwent thrombolysis had an increased risk of stroke, major bleeding, and peripheral thromboembolism within 30 days after the procedure. However, it should be noted that thrombolysis is considered a less serious procedure compared to surgery. Based on the evidence obtained, no method is superior to the other, and the decision in each case must be made taking into account the individual characteristics of the patient, the qualifications of the surgeon and the resources of the hospital.

Subsequent Cochrane reviews compared methods of thrombolysis [40]. Intra-arterial thrombolysis has been found to be more effective than intravenous thrombolysis, which is also associated with a higher risk of bleeding. Thrombolysis was most effective when the catheter was placed in the thrombus. "High dose" and "forced infusion" therapy facilitates thrombus clearance but does not affect amputation rates or the need for additional procedures. Further research is needed to select the optimal technique.

There are a large number of thrombolytic drugs for the treatment of acute limb ischemia. Data from a recent Cochrane review suggest that intra-aortic administration of recombinant tissue plasminogen activator (rt-PA) is more effective in restoring vascular patency compared to intravenous rt-PA or intra-aortic streptokinase [41]. The number of hemorrhagic complications does not depend on the type of therapy. This review included small studies, so it is difficult to make firm recommendations. The use of thrombolysis for graft occlusion in patients with PAD is somewhat different. This method has been used for many years and in most cases is effective as a single procedure. However, some patients require surgical and endovascular intervention [42].

In conclusion, thrombolysis plays an important role in the treatment of CLLI and graft occlusion. The most effective is considered to be intra-aortic administration of thrombolytics. Further research is needed to determine the optimal drug and administration technique. With the accumulation of evidence-based experience in the future, preference is given to new endovascular techniques.

13. Conclusion

PAD is atherosclerotic in nature and is associated with high levels of morbidity and mortality, both due to arterial pathology and an increased risk of cardiovascular events. Critical ischemia of the lower extremities is the final stage of the disease. Drug therapy plays an important role in the correction of risk factors for the secondary prevention of cardiovascular complications. The role of drug therapy in the treatment of symptoms and complications of limb hypoperfusion has been less studied. Surgical and endovascular revascularization are the main treatments for CLLI, but medical therapy may be prescribed as an adjunct to surgical methods or in patients who are not eligible for surgery. New drug approaches using growth factors, stem cells, and gene therapy are currently being explored, opening up new prospects for conservative therapy in the future

Compliance with ethical standards

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Disclosure of conflict of interest

No conflict of interest.

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