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MODERN METHODS OF STIMULATION OF ANGIOGENESIS IN PATIENTS WITH CRITICAL LIMB ISCHEMIA (REVIEW)

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Abstract

The term "critical ischemia of extremities" (critical limb ischemia) was first introduced by P.R.F. Bell in 1982 to refer to a group of diseases accompanied by pain in the legs at rest, trophic ulcers and distal necroses of the lower limbs. Critical ischemia of the lower limbs is a condition of almost complete cessation of arterial blood flow to the tissues of the lower limbs. If the arterial blood supply is not improved, limb amputation becomes inevitable for all patients. Treatment of ischemia of the lower extremities should be complex and differentiated depending on the stage and features of the course of the disease. Modern approaches to the therapy of lower limb ischemia include conservative and surgical methods of treatment, all of which are aimed at improving blood flow in the affected limbs. In the article modern methods of stimulating angiogenesis in patients with lower limb ischemia and results are shown.

Keywords: critical limb ischemia, cell therapy, gene therapy, angiogenesis stimulation

Topicality

Critical limb ischemia (CLI) is a severe form of peripheral artery disease associated with high morbidity and mortality. The problem of obliterating vascular disease ceases to be relevant, annually diagnosed with a frequency of 500-1000 cases per 1 million population in Europe and North America. The prevalence of chronic lower limb ischemia reaches 3% of the world population, in people aged over 50 years in 9-10% of cases and in persons over 60 years - 35-50% [1]. The number of people with CLI growing and in the near future will reach 5 to7% of the population [2]. The frequency of amputations in patients with vascular pathology in Ukraine and abroad reaches 59% and the mortality rate reaches 48%. This disease mostly progresses [3]. According to TASC, among patients with CLI from 10 to 30% live less than 6 months, and 25-30% of patients may need a "big" amputation [4, 5]. If untreated for 1 year one-quarter of patients die, one third will have to undergo amputation of one or both legs, while others will live with both limbs. After 5 years, more than half of patients with CLI will die [6]. In addition, the quality of life of patients with CLI compared with cancer patients in terminal stages and were noticed to be the same. [7].

The goals of treatment of patients with CLI is to increase the distance of walking, healing ulcers, preventing major amputations and improving the quality of life. Currently, treatment options for patients with CLI include endovascular and open revascularization indirect revascularization, amputation [5]. However, despite the availability of treatment options, many patients are poor candidates for endovascular or surgical treatment due to co-morbidities, and through the distal vascular lesions form. The era of gene therapy and cellular mechanisms of so-called therapeutic angiogenesis, emerged to fill the gap treatment options for these patients. Research in the field of therapeutic angiogenesis include complex process of determining appropriate growth factors, dosing and administration. This review summarizes the current results of existing methods of therapeutic angiogenesis as well as finding the best treatment option continues.

History angiogenesis

Angiogenesis is defined as the process of forming new blood vessels from pre-existing blood vessels. Its history can be traced back to the late 19th century. Rudolf Virchow, along with other German pathologist said that human tumors are highly vascularized [8]. In 1939, Sandison, Ide and their colleagues have suggested the presence of a tumor vascular growth factors after they implanted tumors in a rabbit ears and watched the development of new blood vessels. After isolation of the protein, which was active against only mitogenic endothelial cells, Ferrara and his colleagues named the protein vascular endothelial growth

factor (VEGF) in 1989 [9]. In 1992, while studying glioblastomas, Keshet and Plate noted that most ischemic areas of tumors had the highest expression of VEGF [10]. This hypothesis was vital key concept that hypoxia is a trigger for the release of VEGF, which then stimulates angiogenesis.

Gene therapy of CLI

In 90s several research groups have established the role of peptide growth factors to repair venous ulcers. Studies have shown the ability of growth factors to stimulate the healing of neuropathic ulcers provided multiple input and creating high local concentrations. The latter is because the growth factors are rapidly destroyed by proteolytic enzymes in the organism. In this context, the idea of growth factor genes introduction into the genome of cells present in the zone or ulcer ischemia is to ensure a constant expression and creation concentrations close to physiological. As a "conductor" (vectors) genes suggested to use bacterial plasmids, viruses, liposomes, nanoparticles, collagen gels and dressings.

VEGF plays a key role in angiogenesis. This factor selectively stimulates the proliferation and migration of endothelial cells, monocytes and their precursors, increases vascular permeability, promotes vasodilatation via increased production of nitric oxide N0 [11].

Fibroblast growth factor (FGF), hepatocyte growth factor (HGF), angiopoetin (Ang-1), VEGF and HIF-1 is a growth factors, which are the most widely studied as a stimulator of angiogenesis. These growth factors, obtained using encoding gene, promote proliferation of endothelial cells and mainly focus on the endothelial cells.

Isner and others demonstrated introducing gene into plasmid encoding VEGF, in patients with ischemia of the right lower limb, using balloon angioplasty balloon coated phVEGF165 that inflated distally to popliteal artery. Four weeks after the gene therapy, collateral vessels were identified on the level of the knee to the ankle, which confirms the hypothesis that the introduction mitogenes of endothelial cells can stimulate angiogenesis in ischemic limb extremity [13, 14]. Other studies using phVEGF165 was made on 54 diabetic patients with CLI. In this study Kusumanto and others. evaluated the incidence of amputation in these patients after 100 days. Despite the fact that there was no significant reduction in amputation there was significant improvement in other indicators such as ABI and ulcers healing [15].

Fibroblast growth factor-1 (FGF-1) has been studied by TALISMAN researchers (Tenecteplase Versus Alteplase in Ischemic Stroke Management) in 2008. They evaluated the effectiveness of treatment as complete healing of at least one of treated limb ulcers through 25

weeks of observation. Overall 8 injections of FGF-1 were given to treatment group at 1, 15, 30 and 45 days (total of 16 mg of NV1FGF plasmids). In patients receiving NV1FGF noted a slight improvement ulcer healing (19.6%) compared to placebo (14.3%, p = 0.514). However, the tendency to prolong life when using NV1FGF was determined (HR 0,460; P = 0,105) [16]. But, the 2011 study TAMARIS (Efficacy and Safety of XRP0038/NV1FGF in Critical Limb Ischemia Patients With Skin Lesions), in phase 3 randomized clinical trial showed opposite results compared with the study of TALISMAN. Overall, 525 patients from 30 countries were studied in terms of major amputation or death within 1 year. As in the previous study, eight patients received intramuscular injections NV1FGF or placebo in the study ending in 1, 15, 29 and 43 days. There was no significant difference between placebo and treatment group on amputations and mortality (95% CI 0.83-1.49, p = 0.48). The Group has concluded that there is no evidence that FGF-1 is effective in patients with a CLI in relation to the time of amputation and death [17].

Hepatocyte growth factor (HGF) has been studied by Van Belle et al. In terms of models of hind limb ischemia rabbit. They demonstrated that HGF stimulates proliferation and migration of endothelial cells through receptor c-Met. They demonstrated a significant improvement in the formation of collaterals and regional blood flow and reducing muscle atrophy in rabbits hind limb [18]. Interestingly, these results were more clear, while the application VEGF, showed that the combined effect of two growth factors. In studies in patients with critical limb ischemia, they were injected with HGF plasmid to improve limb perfusion (HGF-STAT) and the measured level TcPO2, as an indicator of improved tissue perfusion. Patients received intramuscular injections of high doses compared with medium and low doses of HGF. A group of high dose had higher TcPO2 compared to other groups. However, no differences were observed in the CPI, alleviating pain and healing ulcers [19].

Discovered by Keshet and Pleto elevated levels of VEGF in hypoxic regions of tumors glioblastoma multiforme led to the hypothesis of hypoxia as a powerful trigger of synthesis of VEGF. Hypoxia inducible factor-1 (HIF-1) belongs to a group of transcriptional regulatory protein called hypoxia-induced factors [20]. HIF-1 is the most common and most studied of the group. It was determined that HIF-1 induces many genes, including VEGF expression and other angiopoetins. [20, 21]. Now study currently targeting active expression of HIF-1 transgene in ischemic tissue as a method for therapeutic angiogenesis [21].

New growth factors

Despite the various growth factors discovered, mechanism of angiogenesis in skeletal muscle is unclear. In 2014, several studies investigated proliferator-activated receptor gamma

coactivator (PGC-1). It was found that its presence is needed to complete hypoxic induction of VEGF in the cells of the skeletal muscles. In a study Thom et al. in 2014, transgenic expression of PGC-1 alpha-4 in skeletal muscle in mice induces angiogenesis in vivo. [22]. Interesting that PGC-1 repeats mechanisms of angiogenesis as in physical exercise. Induced blood vessels were more organized, functionally complete compared to the irregular structure of blood vessels, stimulated by VEGF [23]. It was studied by Rove et al. in diabetic mice and is a promising discovery in the field of gene therapy. Furthermore, it was also found that norepinephrine is able to regulate endothelial progenitor cells in ischemic mice rear limb through its various receptors, including alpha-adrenergic receptors and beta 2-adrenergic receptors [24].

Chemokines are a subset of cytokines, which are powerful regulators of leukocyte traffic in both inflammatory and homeostatic processes. Today there are more than 50 chemokines that have been identified, and 20 Chemokine receptors have been cloned [25]. Chemokines are usually associated with multiple receptors, while receptors normally bind to multiple chemokines. Stromal derived factor -1 (SDF-1) is a chemokine, which is also known as CXCL12. It has a multifaceted role in human physiology, including embryonic development and homeostasis. SDF-1 is unique to other chemokines, as it only binds to the receptor CXCR4. SDF-1 has a double effect in vasculogenesis: first, is through the recruitment of CXCR4 endothelial progenitor cells (EPC), and the second is a direct angiogenic effect on endothelial cells. During ischemia, thrombopoietin and other chemokines also cause the release of SDF-1 in platelets and thus facilitate revascularization of ischemic limbs by mobilizing hemangiocytes [26-28]. In studies of SDF-1 in animals in vivo and in vitro has been shown that it improves blood flow and perfusion through the mobilization of endothelial progenitor cells in patients with CLI. During ischemia, the levels of SDF-1 increased, as hypoxia or apoptotic conditions are potent stimulators of induction of chemokine expression. Increased allocation of SDF-1 in ischemic muscle acts as an attractant signal for the CXCR4 receptor EPC. Further increase of EPC processes neovascularisation in ischemic tissues [29 - 31]. Yamaguchi et al. studied the effect of SDF-1 in muscle vasculogenesis in ischemic hind limbs of mice. They noted the increase in EPC via microscopic examination after administration of SDF-1 in muscle. Clinical trials of SDF-1 in patients with CLIs are needed for better understanding of the mechanisms of chemokine, especially SDF-1 action.

Cell therapy of CLI

Twenty years ago it was believed that the formation of new blood vessels is limited to the process of angiogenesis - the formation of new blood vessels from pre-existing vasculature. Also vasculogenesis is the process of blood vessel formation at the site of EPC and vascular progenitor cells. [32]. Asahara and others suggested that EPC may play a role in increasing the formation of collateral vessels in ischemic tissues [33-34]. The discovery of progenitor cells that differentiate into endothelial cells derived from bone marrow, paved the way for cell therapy in the therapeutic angiogenesis.

The first clinical study on the use of stem cells in the treatment of CLI published in 2002 E. Tateishi-Yuyama et al. They examined the effectiveness of implanting of autologous mononuclear cells from the bone marrow (BM MNC) [35]. The results of Research TACT (Therapeutic Angiogenesis by Cell Transplantation) were first published in 2002, followed by a study published in 2008 to assess the long-term clinical outcome. The study showed that autologous transplantation of BM MNC is a safe and effective procedure for therapeutic angiogenesis. In the second part of the study it determined time without mortality and amputation. 3-year term without amputation was 60% (95% CI 46-74), while survival was 80% (95% CI 68-91) [35, 36]. After 2 years, a significant improvement was noted on a scale of pain in the lower limb, the size of ulcers and painfree walking distance. However, ABI and TcPO2 of patients did not differ significantly. [36]. TACT researchers concluded that the development of blood vessels in cell therapy by BM MNC leads to long-term improvement in patients with CLIs and postpones amputation.

In two studies on patients with CLI transplantation of predecessors of endothelial cells in conjunction with the introduction of vascular growth factor was done. The resulting stable effect 6 months after transplantation. The authors also showed the safety and efficiency of the technique [37, 38]. RR Huangetal. (2004) proposed a different approach to autologous transplantation of MNC mobilized from peripheral blood using G-CSF. After 3 months of observation main clinical symptoms improved significantly in more than half of patients. Angiography noted significant improvement in collateral blood flow. However, necessary for obtaining autologous BM MNC from peripheral blood stimulation of BM is a serious burden for the weakened disease organism and is undesirable for many older patients [39]. A double-blind pilot study showed that the use of autologous transplantation of stem cells (SC) of BM reliably leads to a reduction of pain at rest and lengthening the period to amputation in the experimental group compared with the control group that received a placebo in the form of peripheral blood [40]. As the results of preclinical and clinical studies in patients with CLI

transplantation of multipotential stromal cells obtained from autologous adipose tissue is able to stimulate the process of angiogenesis, which leads to a reduction of ischemic impact by enhancing regenerative muscle strength [41]. The cell receiving from autologous adipose tissue is safe and not require any drug stimulation. Later publication of pilot clinical studies of H.C.Lee et al [42] confirm the efficacy and safety of endothelial progenitor cells isolated from adipose tissue. With digital angiography revealed numerous formation of collateral vasculature, resulting in the end of 6 months in 66.7% of patients had a decrease of pain at rest, pain-free and significant increase in walking distance.

Research of stimulation of angiogenesis via subcutaneous application of granulocyte-macrophage colony stimulating factor (GM-CSF) (START) was a double-blind, randomized, placebo-controlled study in 40 patients with peripheral arterial disease, whose goal was to repeat the study of the effect of GM-CSF in coronary blood flow . GM-CSF is used to mobilize BM MNC from peripheral blood in the target tissue. Unfortunately, the pilot study showed that GM-CSF is probably not effective in patients with moderate to severe intermittent claudication in all aspects, including the ABI and painfree walking distance. [43].

Research PROVASA with intraarterial BM MNC introduction in patients with critical limb ischemia in phase II was a double-blind, randomized study in patients with CLI. Research has shown that cell therapy was associated with improved healing of ulcers (ulcer area, 3.2 +/- 4.7 cm 2 to 1.89 +/- 3.5 cm2 [P = 0,014], compared to placebo 2, 92 +/- 3.5 +/- 2.89 cm2 to 4.1 cm2 [P = 0,5]) and reduce pain (5.2 +/- 1.8 to 2.2 +/- 1, 3 [P = 0,009], compared with placebo, 4.5 +/- 2.4 to 3,9 +/- 2,6 [P] = 0,3) for 3 months. [44]. Unfortunately, the study did not achieve its clinical endpoint. It showed a slight increase in the ABI in the treatment group.

Conflicting results of the efficacy of bone marrow cells in patients with CLI study showed JUVENTAS. Research JUVENTAS was a large, randomized, double-blind, placebo-controlled study, which was designed to determine whether the effective re-infusion of autologous BM MNC in the common femoral artery of patients with CLI. Indicator of effectiveness was the prevention of amputation or limb preservation. 160 patients were randomized and treated with BM MNC or placebo. The control group received repeated infusions of BM MNC in common femoral artery three times at 3-week intervals. The study did not reveal any significant differences between the control group and placebo on the primary outcome. The level of the amputation in treatment group -19% versus 13% in the placebo group. However, the rate of amputations did not meet statistical significance (RR 1,46; 95% CI 0.62-3.42). Security - all-cause mortality, the occurrence of malignancies, or

hospitalization due to infection - no significant difference between groups (RR 1, 46, 95% CI 0.63-3.38). Quality of life, rest pain, ABI and TcPO2 in the control group compared with placebo were improved. However, once again, there was no significant difference. [45, 46].

Another method understudied in terms of use in vascular surgery is the use of platelet rich plasma (PRP). "The buzz around PRP clearly came to science," said Wellington Hsu, MD, associate professor of orthopedic surgery and neurosurgery at Northwestern University Feinberg School of Medicine - "In medicine, we rely on scientific evidence to support best use of treatments, but with PRP that hasn't been the case. Interest in PRP jumped way ahead of the research. ". PRP does not contain any drugs or chemicals. "PRP is completely natural and uses their own blood platelets patient to enhance the biological healing process in the body," said Michael Terry, MD, associate professor of orthopedic surgery at Feinberg School of Medicine, "-There are very few documented complications associated with the PRP, it is a safe method, and it has shown good results in many cases.". Seven major growth factors contained in the platelet rich plasma: platelet-derived growth factor (PDGF-aa, PDGF-bb, PDGF-ab), transforming growth factor (TGF-β1, TGF-β2), vascular endothelial growth factor (VEGF) and epithelial growth factor (EGF). These natural growth factors are in biologically pre-defined ratios [47].

Conclusions

The emergence of molecular biology research and a better understanding of the mechanism of angiogenesis gave rise to the development of therapeutic angiogenesis as a viable and promising strategy for treating patients with CLI. Studies using animal models in the treatment of growth factors and cell based therapies for CLI slowly but surely led to clinical trials. Potential angiogenic growth factors such as VEGF, HGF, FGF, HIF-1, and chemokines were evaluated in clinical trials in humans, even with mixed results. The same is true for cell therapy. Contradictory and inconclusive results of clinical trials should be an incentive for further gradual and large randomized clinical trials in humans using various growth factors or cell therapy. Currently, the therapeutic armory of CLI patients who are not candidates for direct operative revascularization remains limited.

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