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PATHOGENETIC APPROACH TO THE TREATMENT OF WOUNDS AFTER AMPUTATION OF THE FOOT AGAINST THE BACKGROUND OF CHRONIC LIMB-THREATENING ISCHEMIA (CLTI)

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SUMMARY. The strategy of treatment of chronic limb-threatening ischemia (CLTI) should be its timely revascularization and prioritization of performing "small" amputations on the foot.

The aim – to improve the healing of wounds after amputation of a part of the foot with the help of a biological membrane enriched with growth factors for their subsequent autodermoplasty

Material and Methods. 81 patients with IV grade CLTI were under observation according to the Fontaine classification (category 6 according to the Rutherford classification), with open wounds after amputation of a part of the foot due to dry gangrene. The average age of the patients was 56.7±9.3 years, all men. Patients underwent vasoballoon angioplasty of the arteries of the lower extremities. After that, amputation of the foot was performed using various methods. In connection with the shortage of skin flaps of the wound, 41 patients were treated by the open method, according to the traditional method, followed by autodermoplasty. In other patients (40 patients), to stimulate the reparative process, the entire area of the wound surface on the foot was covered with a plasma membrane (PRGF®-Endoret® supernatant), enriched with growth factors. To control the regeneration process, the tyrosine kinase index was calculated at different times of treatment (6-10 and 15 days after amputation). Also, the content of interleukins IL-1β, IL-4, tumor necrosis factor (TNF-α), interferon (IFN-γ) was determined. After that, the intercytokine coefficient (ICC) was calculated.

Result. In patients who underwent endovascular angioplasty and PRP therapy before limb amputation and closed the wound with a plasma membrane, ICC decreased below baseline. This can be explained by a significant increase in the level of anti-inflammatory cytokines against the background of a stable amount of pro-inflammatory factors. The reaction of IL-4 and IFN-γ can be regarded as preparation for the transition of the wound process to the proliferation stage, and the decrease in the levels of IL-1β and TNF-α reflects a decrease in the manifestations of the inflammatory reaction in the wound.

Conclusions: 1. Wound healing after foot amputation in patients with CLTI depends not only on restoration of blood supply to the limb. The healing process in an acute wound is largely controlled by the spatio-temporal action of growth factors, cytokines, and chemokines.

2. The use of plasma membrane as a biological membrane enriched with growth factors (PRGF)-Endoret can be a new therapeutic strategy to accelerate the healing process of wounds after amputation of the foot on the background of CLTI with the purpose of subsequent autodermoplasty.

KEY WORDS: Chronic threatening ischemia of the lower extremities; amputation of the foot; plasma enriched with growth factors; tyrosine kinase index.

Introduction. More than 200 million people worldwide suffer from occlusive diseases of peripheral arteries. These disease rates are expected to increase as increased the final stage of this disease, which is chronic limb-threatening ischemia (CLTI). It affects 11 % of patients with peripheral artery disease and is associated with high rates of limb loss (multiple limb amputation rates in patients with CLTI reach 40% at 6 months) and mortality, as well as high treatment costs [1–5].

In recent years, the interventional treatment of CLTI has changed significantly: endovascular revascularization has become dominant in the treatment strategy of this pathology. Moreover, the introduction of multidisciplinary approaches to save the limb increases the chances of successful ulcer healing, subsequently preventing wound recurrence or amputation [6].

Therefore, the exact determination of the severity of the threat to the limb should be fundamental and based on the classification of wounds, ischemia and infection of the foot (WIfI). Evidence-based revascularization is based on three independent axes: patient risk, limb severity, and anatomical complexity (PLAN) [7]. Thus, the treatment strategy for CLTI should be timely revascularization of the limb and prioritization of "small" foot amputations.

At the same time, the treatment of open wound surfaces arising after amputation of a part of the foot remains an actual problem. It should be noted that wound healing, especially after amputation, is a complex process involving various immune and structural cells, in particular, their secretion of cytokines, chemokines, and growth factors that regulate the healing phases [8, 9].

To date, several immunomodulatory approaches have been used, targeting both inflammatory factors: TNF-α, IL-1, the NF-κB pathway, and anti-inflammatory factors such as IL-4, IL-10, and TGF-β were used for tissue repair and regeneration [10, 11]. In this regard, the regulation of immune cells by modulating the expression of various cytokines and deli-

very of growth factors to the wound is a promising strategy in wound healing.

Materials and methods. 81 patients with IV grade CLTI were under observation, according to the Fontaine classification (category 6 according to the Rutherford classification), with open wounds after amputation of a part of the foot due to dry gangrene. The average age of the patients was 56.7±9.3 years, all men. Previously, for the purpose of revascularization, patients underwent vasoballoon angioplasty of various segments of arteries of the lower extremities affected by the obliterating process. After that, foot amputation was performed: according to Garangeau - in 10 patients, according to Chopar – in 51 cases, according to Lisfranc or Lisfranc-Haye – in 19 patients.

Patients were divided into three groups. In connection with the shortage of skin flaps of the wound, 41 patients were treated by the open method, according to the traditional method, followed by autodermoplasty (the first group). The second group consists of 40 patients who, three weeks before the restoration of blood supply in the limbs, underwent "therapeutic" neoangiogenesis with plasma enriched with growth factors (PRGF®-ENDORET®), prepared according to the protocol of the Institute of Biotechnology (Spain) [12]. Blood was taken by venipuncture from the cubital vein. Blood was collected according to the Endoret PRGF protocol into 9 mm sterile tubes containing 3.8% (w/v) sodium citrate. Using Endoret's proprietary technology, collected blood was centrifuged at 460× g for 8 min at room temperature using a PRGF-Endoret System Centrifuge to obtain PRGF. The blood was separated into three fractions: plasma containing mainly platelets (upper layer – F1), a layer of white blood cells "leukocytes" (middle layer – F2) and erythrocytes (lower layer – F3). PRGF was then selected in two fractions designated as F1 and F2. F1 was used for paravasal management (Fig. 1).

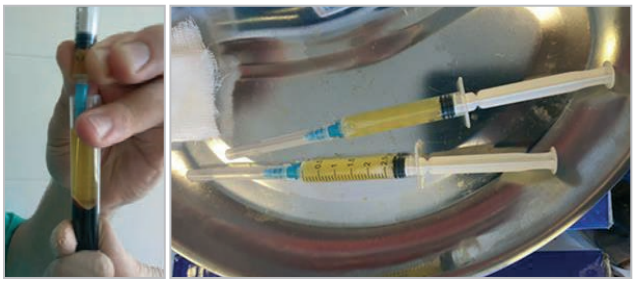

Fig. 1. Blood collection method for PRP therapy.

It was injected paravasally in 2 ml units under ultrasound guidance, in the location of the main vessels of the lower leg affected by the atherosclerotic process (a.tibialis posterior and a.tibialis anterior (Fig. 2)).

Also, in this group of patients, on the 5-6th day after amputation, to stimulate the reparative process, the entire area of the wound surface on the foot was

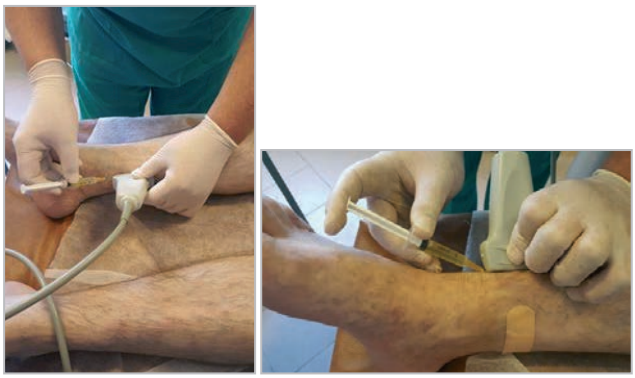

Fig. 2. The technique of performing PRP therapy under ultrasound navigation in the projection of the lower leg arteries.

covered with PRF (Platelet-reach fibrin) plasma membrane (PRGF®-Endoret® supernatant), enriched with growth factor. For PRF therapy, the patient's blood was centrifuged at a speed of 3000 rpm for 10–12 minutes in test tubes that were located at an angle of forty degrees with a calcium chloride plasma activator at the rate of 50 µl of PRGF ® activator per ml of the drug, in order to achieve degranulation of platelets and the release of growth factors. The resulting bundle of blood plasma was transferred to the PRF-Box for 10–15 minutes to obtain a fibrin membrane (Fig. 3).

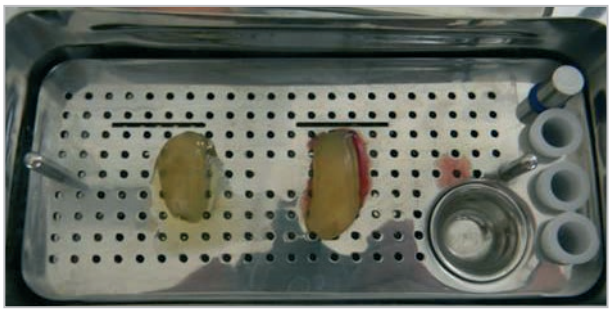

Fig. 3. PRF membranes are prepared for transplantation on the surface of the wound.

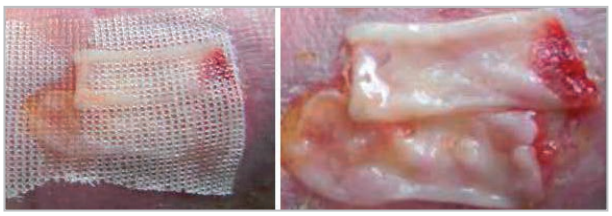

Fig. 4. Closing the PRF wound with a plasma membrane.

The third group (control) – 13 patients with signs of CLTI, but without necrotic changes on the foot.

With the help of biochemical and immunological studies, the peculiarities of the pathogenetic mechanisms of the healing process of wounds on the foot after amputations were evaluated, the reactivity of cells was evaluated by calculating the tyrosine

kinase index (TKI – the ratio of tyrosine kinase activity to tyrosine phosphatase activity) at different times of treatment (6–10 and 15 days after amputation). The content of interleukins IL-1β, IL-4, tumor necrosis factor (TNF-α), interferon (IFN-γ) in the blood plasma was determined by the radioimmunoassay method using a standard commercial set of reagents from the company "Amersham Pharmacia Biotech UK Limited", after which the intercytokine coefficient was calculated (ICC) – the ratio of the relative increase (in %) of the level of cytokines of the damage phase (IL – 1β and TNF – α) to the increase of the level of cytokines of the proliferation and remodeling phase (IFN-γ and IL-4), compared to the baseline before the operation according to the formula:

$$\mathrm{ICC}=\frac{(\Delta IL{-}1\beta{+}\Delta TNF{-}\alpha)}{(\Delta IF{-}\gamma{+}\Delta IL{-}4)}$$

ICC can reflect the reactivity of systemic mechanisms that limit the phase of alteration in the wound and induce proliferative processes in the wound.

We also determined the dynamics of the wound process on the foot using a cytological analysis of the cellular composition of the wound by the fingerprint method. The regenerative-degenerative index was used to assess the severity of degenerative and regenerative processes in the wound. Cytological examinations of the wound were performed after 2, 4, 8, 14 days after the amputation of the foot.

The obtained results were analyzed using the STATISTISA 12.0 program package. The significance of the obtained differences between the results (minimum level of significance $p<0.05$) was evaluated using the Kruskel-Wallace and Newman-Keuls tests (BioStat program, AnalystSoft Inc).

Results. According to our data, the tyrosine kinase index (TKI) reflects the sensitivity of cells to factors that stimulate the processes of proliferation, migration and intercellular interactions in damaged tissues and can be used as an informative criterion for the prognosis of wound healing. However, a clearer answer to the presence of other factors affecting reparative processes in the wound can be given by the definition of cytokines, because it is they who regulate intercellular interactions that are specific for each phase of the wound process [13, 14]. Our studies found that the cytokine levels in blood plasma before foot amputation were almost identical in the first and second group of patients compared to the third group. At the same time, in the 1st and 2nd group of patients, we found a significant increase in the level of TNF-α (compared to the control group of patients, by 5.1 and 1.2 times, respectively). The content of other cytokines in the first and second groups practically did not differ. ICC in these groups of patients with necrotic lesions of the foot was lower than the control by 57.8%, respectively. This may indicate metabolic changes in the production of cytokines associated with necrotic processes in the foot.

Table 1. The initial content of cytokines (mg/ml) in the blood plasma of patients (M±m) of the experimental groups

A group of patients	IL-1β, mg/ml	IL-4, mg/ml	TNF–α, mg/ml	IF–γ, mg/ml
Control	807.72±20.59	8.54±0.73	23.46±2.29	45.27±4.15
1st	526.60±18.95**	3.77±0.19***	96.87±5.06***	10.41±0.89***
2nd	554.32±39.81	3.56±0.42***	118.80±8.93***	9.76±1.01***

Note: * – p<0.05. ** – p<0.01. *** – p<0.001 comparing to the control group.

At the same time, in the 1st and 2nd group of patients, we found a significant increase in the level of TNF-α (compared to the control group of patients, by 5.1 and 1.2 times, respectively). The content of other cytokines in the first and second groups practically did not differ. ICC in these groups of patients with necrotic lesions of the foot was lower than the control by 57.8%, respectively. This may indicate metabolic changes in the production of cytokines associated with necrotic processes in the foot.

We analyzed the dynamics of ICC in patients whose wounds were treated according to the standard method and according to the method of PRF therapy. It is interesting that in the patients of the first group of patients, ICC increased by an average of 3.9 times compared to the foot amputation, mainly due to IL-1β and TNF-α. This may be evidence of the deterioration of alternative processes and the spread of destructive changes in the wound. At the same time, low levels of IL-4 and IFN-γ are evidence of a decrease in the reserve capacity of pro-inflammatory factors. Such a situation can be explained by insufficient blood supply to the foot and its ischemia. In patients who underwent endovascular angioplasty and PRP therapy before limb amputation and wound closure with a plasma membrane, ICC decreased below baseline. Such dynamics can be explained by a significant increase in the level of anti-inflammatory cytokines against the background of a stable amount of pro-inflammatory factors. Thus, the reaction of IL-4 and IFN-γ can be regarded as preparation for the transition of the wound process to the proliferation stage,

and the decrease in the levels of IL-1β and TNF-α reflects a decrease in the manifestations of the inflammatory reaction in the wound.

Thus, the activity of the tyrosine kinase system, as well as the peculiarities of the cytokine relationship, which is a reflection of the processes of alteration and proliferation in the wound, can be an objective criterion for the "readiness" of skin autotransplantation on the wound surface.

The results of cytological studies showed that the use of the above-mentioned technology led to a decrease in the number of cells that determine the acute phase of inflammation (neutrophils, lymphocytes, monocytes) and an increase in the number of cells responsible for reparative processes (macrophages, fibroblasts) in smears-prints of wounds. For example, in patients already on the 2nd-3rd day, a decrease in the content of neutrophils and lymphocytes was noted, on the 4th-5th day - in all inflammatory cells. This corresponds to the transition from the degenerative-inflammatory type of cytograms to the inflammatory-regenerative type. By the 8th day, a change in the nature of the cytograms to the regenerative-inflammatory type is noted in most patients. At the same time, in patients whose wounds were treated according to traditional methods, the change in the character of cytograms to the regenerative-inflammatory type occurs much later, on 18-21 days. The above is an additional criterion for performing autodermal plastic surgery of a foot wound.

Discussion. There is no doubt that the use of shunting or endovascular methods of limb revascularization in CLTI, especially in the presence of necrosis on the foot, is an optimal and effective means of preventing limb amputation [15]. It is undeniable that the indications for limb revascularization in CLTI should be based on the assessment of the patient's condition, the severity of the necrotic lesion of the limb (WIfI classification) and angiographic study data [7]. In our opinion, arterial reconstruction according to the angiosomal theory and restoration of blood flow to the target artery may be indications for performing "small amputations" of the foot under conditions such as: a) increase in skin temperature on the side of the lesion according to the angiosomal principle of blood supply to the lower extremities on the anteromedial, posteromedial, and posterolateral surfaces of the leg, at the levels of its lower and middle thirds, on the medial and rear surfaces of the foot; b) improvement of the condition of the microcirculatory channel by means of the study of the partial pressure of oxygen (tcpO2) in the soft tissues of the lower limb (transcutaneous oximetry) on the foot; c) improvement of tissue perfusion, confirmed by laser flowmetry; d) increase of the Ankle Brachial Index (ABI)[6].

Undoubtedly, the improvement of blood supply to the distal parts of the limb creates favorable conditions for the healing of the wound formed after the amputation of a part of the foot. However, there are differences in the healing of wounds depending on their location on the foot. Thus, foot amputations according to Garangeau, patients, Chopard, Lisfranc, or Lisfranc-Haye will create large wound surfaces extending to the forefoot or midfoot along with the dorsum or plantar. Such wounds are considered the most difficult type for healing (their healing time takes 2–3 months on average) [16] and the wound process in them takes place according to the type of chronic wound. Despite differences in etiology at the molecular level, chronic wounds share certain common features, including excessive levels of pro-inflammatory cytokines, proteases and senescent cells, as well as the existence of persistent infection and stem cell deficiency. According to the data of scientific studies, in chronic wounds, pro-inflammatory cytokines interleukin-1, interleukin-6 and tumor necrosis factor-alpha are present in much higher concentrations in the wound fluid of non-healing ulcers, which demonstrate a persistent phase of inflammation, which prevents the transition to the formation of granulation tissue [17, 18, 19].

The results of our research show that after amputation of the foot in patients, the level of ICC increases due to an increase in IL-1β and TNF-α, which may indicate the deterioration of alternative processes and the spread of destructive changes in the wound, and low levels of IL-4 and IFN-γ is evidence of a decrease in the reserve capacity of pro-inflammatory factors. The above indicates that the wound healing process can become chronic. At the same time, the active tactics of managing open wounds after amputation of the foot, proposed by us, using the application to their entire surface of PRF (Platelet-reach fibrin) of the plasma membrane (PRGF®-Endoret® supernatant), enriched with a growth factor, creates optimal conditions for the course of the wound process in its first and second phases due to the release of growth factors [20–24]. This is confirmed by the data of our research. Thus, in patients who underwent endovascular angioplasty and PRP therapy before limb amputation and wound closure with a plasma membrane, ICC decreased below baseline. Such dynamics can be explained by a significant increase in the level of anti-inflammatory cytokines against the background of a stable amount of pro-inflammatory factors. Also, the reaction of IL-4 and IFN-γ can be considered as preparation for the transition of the wound process to the proliferation stage, and the decrease in the levels of IL-1β and TNF-α reflects the decrease in the manifestations of the inflammatory reaction in the wound. Taking this

into account, the activity of the tyrosine kinase system, as well as the peculiarities of the cytokine relationship, which is a reflection of the processes of alteration and proliferation in the wound, can be an objective criterion for the "readiness" of skin autotransplantation on the wound surface.

Conclusions: 1. Wound healing after foot amputation in patients with CLTI depends not only on restoration of blood supply to the limb. The healing process in an acute wound is largely controlled by the spatio-temporal action of growth factors, cytokines, and chemokines.

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Prospects for further research. Although there are many scientific studies in the scientific literature on the above topic, larger studies with clinical trials and specific protocols are needed to clearly establish the beneficial effects of PRP and PRF, as well as the exact mechanisms of their effects on wound healing.

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ПАТОГЕНЕТИЧНИЙ ПІДХІД ДО ЛІКУВАННЯ РАН ПІСЛЯ АМПУТАЦІЇ СТОПИ НА ТЛІ ХРОНІЧНОЇ ЗАГРОЗЛИВОЇ ІШЕМІЇ НИЖНІХ КІНЦІВОК

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РЕЗЮМЕ. Стратегія лікування хронічної загрозливої ішемії нижніх кінцівок повинна полягати у своєчасній її реваскуляризації та наданні пріоритету виконання «малих» ампутацій на стопі.

Мета – покращити загоєння ран після ампутації частини стопи за допомогою біологічної мембрани, збагаченої факторами росту, для наступної їх автодермопластики.

Матеріал і методи. Під спостереженням перебував 81 хворий із CLTI IV ст. за класифікацією Fontaine (6 категорія за класифікацією Rutherford), із відкритими ранами після ампутації частини стопи з приводу сухої гангрени. Середній вік пацієнтів складав (56,7±9,3) роки, всі чоловіки. Пацієнтам було здійснено вазобалонну ангіопластику артерій нижніх кінцівок. Після чого виконана ампутація стопи за різними методами. У зв'язку із дефіцитом шкірних клаптів рани, 41 пацієнт лікувався відкритим методом, за традиційною методикою, з наступною автодермопластикою. У інших хворих (40 пацієнтів) для стимуляції репаративного процесу вся площа ранової поверхні на стопі покривалась плазматичною мембраною (супернатант PRGF®-Endoret®), збагаченою факторами росту. Для контролю за процесом регенерації розраховували тирозинкіназний індекс у різні терміни лікування (6–10 та 15 доба після ампутації). Також визначали вміст інтерлейкінів IL-1β, IL-4, фактора некрозу пухлин (ФНП-α), інтерферону (ІФН-γ), після чого вираховували інтерцитокіновий коефіцієнт (ІЦК).

Результат. У хворих, в яких до ампутації кінцівки була виконана ендоваскулярна ангіопластика та PRP-терапія і здійснено закриття рани плазматичною мембраною, ІЦК знижувався нижче вихідного, що можна пояснити значним збільшенням рівня протизапальних цитокінів на тлі стабільної суми прозапальних факторів. Реакцію IL-4 та ІФН-γ можна розцінювати як підготовку до переходу ранового процесу до стадії проліферації, а зниження рівнів IL-1β та ФНП-α відображає зменшення проявів запальної реакції в рані.

КЛЮЧОВІ СЛОВА: хронічна загрозлива ішемія нижніх кінцівок; ампутація стопи; плазма, збагачена факторами росту; тирозинкіназна система.

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