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TREATMENT OF CHRONIC WOUNDS OF PATIENTS WITH DIABETES MELLITUS USING HETEROGRAFTS

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The aim. *To investigate the reduction of wound healing time of various etiologies on the background of diabetes mellitus with arteries and veins with the help of combined treatment with the use of heterografts.*
Material and Methods. *The article uses the results of treatment of 18 patients with chronic wounds of different etiology with diabetes which were treated in the department of vascular disease in "Institute of General and Emergency Surgery Named after V. T. Zaitsev NAMS of Ukraine" in 2019–2020 years. All patients had diabetes of II type, and 8 of them had III and IV level of limb ischemia according to Fontaine, and 7 of them had chronical venous insufficiency (CVI) C6 (according to CEAP), and 2 patients were diagnosed arterial and venous pathologies, one patient had vast chronic post-traumatic wound of a shin. All patients underwent analysis of clinical, laboratory, non-invasive and invasive methods of patients' examination to determine the degree of the main blood flow disturbance, the nature of collateral blood circulation and microcirculation of the level of wound contamination, as well as the phase of the wound developing. Among the patients of the studied group with CVI, 2 patients underwent femoral shin shunting, 2 patients underwent hybrid reconstructive surgery, and 4 patients underwent endovascular interventions on the shin's arteries. Patients with CVI underwent sclerooblitteration of disabled perforators under ultrasound navigation. The patients were prescribed the following scheme: compensation of diabetes, metabolic therapy, antibacterial, anticoagulant and angiotropic therapy, physical therapy, local treatment: photodynamic therapy and staged closure of tissue defects by a heterograft membrane.*
Results. *The area of wounds surface in the patients with obliterating lesions of the arteries of the lower extremities before the start of treatment was in average of 391.3±100.42 cm^2, against the background of complex treatment and wound closure with a heterograft on days 10–12 of treatment – 4.72±0.63 ($p<0.01$), and complete closure of the wounds was achieved within 3 weeks. In the patients with chronic venous insufficiency after performing sclerobliteration of incompetent perforants and PDT, the wound area was 16.92±0.18 cm^2, on days 7–10 – 7.82±0.68 3 (by 50.63 %, $p<0.01$), and complete healing of the tissue defect was reached by the 4th week.*
Conclusions. *Use of a heterograft, namely the amniotic membrane makes it possible to achieve shorter periods of healing of chronic wounds in patients with diabetes mellitus. The healing is 2–3 times faster than other modern methods of treatment. It reduces cost of treatment and reduces the period of disability. Shorter treatment period also reduces workload on medical staff and improve the quality of life of patients with diabetes mellitus. Faster wound cleaning lowers risks of local infectious complications*
Keywords: *diabetes, chronic wounds, limb ischemia, chronic venous insufficiency, heterograft*

1. Introduction

Patients with diabetes mellitus (DM) have a number of serious and costly complications, such as diabetic nephropathy, retinopathy, and foot lesions. Pathological conditions that lead to the formation of chronic wounds of the lower extremities in patients with DM are diverse, among them the most common are injuries, neuropathy, chronic arterial insufficiency (CAI) and chronic venous insufficiency (CVI) lower extremities, pyoderma, erysipelas and others. Less often, cancers, systemic connective tissue diseases and a number of other diseases lead to the formation of chronic wounds. As a rule, the conditions of chronic wound formation are: repeated trauma, a classic example of which is neuropathic foot ulcers in patients with DM, ischemia (neuro-ischemic and ischemic forms of diabetic foot syndrome), the presence of chronic persistent local infection, excess protease production in the wound and activity of growth factors [1]. Any chronic wound is characterized by a combination of the following clinical signs: the presence of necrosis, lack of healthy granulation tissue, sagging marginal epithelialization, inability to heal under the scab [2].

Peripheral vascular pathology is one of the determining factors influencing the healing of ulcerative defects of the extremities. The state of critical limb ischemia (CLI) deserves special attention, as it has a real threat of amputation. In patients with DM, CLI is five times more common than in people without DM. CLI and ankle-brachial index (ABI)<0.5 are indications for surgical correction of blood flow. Tactics and type of surgical treatment are determined taking into account the topical localization, distribution and severity of occlusive lesions of the arteries [3].

Along with neuropathy and lack of peripheral blood flow, one of the reasons is that wounds that do not heal for a long time in diabetic foot syndrome is a chronic infection that requires long-term use of expensive antibiotics and antiseptics. Most modern dressings create

an adequate barrier, preventing secondary infection of the wound from the surrounding skin and thus reducing the time and cost of treatment. Infection with DM is a threatening condition for the limb, which is the cause of emergency amputations in 25–50 % of cases. In most cases, the causative agents of superficial infections are gram-positive cocci, and deep infection, especially in the presence of necrosis on the background of ischemia, is partially polymicrobial and is associated with aerobic and anaerobic grams of positive and grams of negative microorganisms [4].

The basis of treatment of chronic wounds at DM is achievement of compensation of a carbohydrate metabolism which is reached by correction with sugar-lowering therapy. In the presence of infectious complications, ischemic lesions and hyperglycemia, patients need to switch to insulin therapy. Thus, hyperglycemia, which exceeds 10 mmol/l, not only prevents wound healing, but also enhances immunosuppression [5].

The basis of treatment of local infection is the appointment of adequate antibacterial therapy in combination with local surgical treatment, which includes necrectomy and drainage of the purulent lesion [6]. Much attention is paid to the unloading of the affected limb, without which the epithelization of the ulcer defect in the sole is unlikely [7].

Topical treatment includes surgical treatment of the wound defect, mechanical or chemical removal of necrotic tissue and fibrin plaque, treatment of the wound edge and removal of hyperkeratosis, opening and drainage of purulent infusions, and the use of special dressings. Regular local treatment of neuropathic ulcers includes removal of hyperkeratoses, which prevent the development of marginal epithelialization and closure of the wound edges. Recently, the theory of wound base treatment "Wound Bed Preparation" was formulated [8] – a strategy of wound treatment to transition from chronic to acute wound and removal as a necrotic component, consisting of necrotic tissue and phenotypically altered cells of the edge and base of the wound. and the exudate produced by them. The theory was based on the study of cell lines from the edge of the wound. The following cell changes were detected, namely inhibited proliferation and decreased functional activity of keratocytes and fibroblasts, as well as proteases that destroyed the extracellular matrix. Fibroblasts cultured from chronic wounds are aging, have low proliferative activity and are not sensitive to cytokines, including growth factors [9]. It should be noted that the term "necrectomy" is a process of removing from a (chronic/acute) wound necrotic tissue, fibrin, bacteria, is the narrowest concept, both theoretically and practically. It is the treatment of the bottom of the wound that helps to translate the chronic wound into an acute state and is the basis for the activation of endogenous processes of tissue regeneration. The need for such aggressive treatment is dictated by the following reasons:

1) the presence of necrotic tissue, fibrin film is a potential substrate for the development of infectious complications;

2) cell lines at the edge of the chronic wound undergo phenothepic transformation, which leads to disruption of regeneration. Treatment is possible in several ways: surgical treatment, autolytic and chemical cleaning of the wound, mechanical necrectomy.

Currently, autolysis is carried out mainly through the local use of hydrogels. Significant disadvantages of this tactic – high cost, low speed of cleaning, the risk of infectious complications, limited use in neuro-ischemic forms of diabetic foot syndrome. Moreover, autolysis provides only partial wound cleansing.

The main requirements for bandages used in treatment:

– ability to retain moisture, because wound healing is possible only in its natural moist environment;

– ability to absorb or not disrupt the outflow of exudate;

– ability to create a bacterial barrier, thus preventing secondary infection;

– ability to provide thermal insulation;

– trauma.

Achieving a positive result can often be achieved only with a multidisciplinary approach (joint management of patients by angiosurgeons, orthopedists, purulent surgeons, endocrinologists, cardiologists). Despite the emergence of new drugs, means of local wound therapy, expanding the possibilities of vascular surgery, a positive result can be achieved only with a multidisciplinary approach.

The aim of the study was to evaluate the reduction of wound healing time of various etiologies against the background of diabetes mellitus with arterial lesions and chronic venous insufficiency with the use of multicomponent treatment and the use of heterografts.

2. Materials and methods

The results of treatment of 18 patients with chronic wounds of various etiologies on the background of DM, who were treated in the Department of Acute Vascular Diseases at the "V. T. Zaitsev Institute of General and Emergency Surgery National Academy of Medicine of Ukraine" in 2019–2020. The average age of patients was 67±3.6 years, the duration of DM – 11±1.4 years. All patients suffering from type II DM, 8 of them had III–IV degree of limb ischemia according to Fontaine, 7 – chronic venous insufficiency (CVI) C6 (according to CEAP classification), two patients were diagnosed with a combination of arterial venous pathology, one patient had extensive chronic post-traumatic shin wound.

In all observations, patients signed an agreement to participate in the study. The entire list of studies and methods of treatment used was approved by the ethics commission of the State Institution "V. T. Zaitsev Institute of General and Emergency Surgery National Academy of Medicine of Ukraine", protocol No. 5.b from 16.01.2019.

Analysis of clinical, laboratory, non-invasive and invasive methods of examination of patients allowed to determine the degree of violation of the main blood flow, the nature of collateral circulation and microcirculation

of the level of wound contamination, as well as the phase of the wound process. Diagnosis was performed on all patients according to a standard algorithm:

1. History, clinical and laboratory research: duration of the disease, analysis of laboratory research methods and history of comorbidities.

2. Non-invasive study included:

– determination of the index of regional systolic pressure (IRSP) on the arteries of the foot using a portable ultrasound machine "Super Dopplex" (China);

– ultrasound dopplerography using the device "Hitachi EUB 7500" (Japan) with a linear sensor L 5–10 MHz;

– transcutaneous oxygen voltage ($T_{cp}O_2$) in tissues of foot by means of the TSM 400 device of production "Radiometer Copenhagen" (Denmark);

– to assess the effectiveness of local treatment were used the results of cytological studies of prints from wounds and microbial contamination of tissues of the purulent focus (studied the qualitative and quantitative composition of the microflora, sensitivity to antibacterial drugs);

– planimetric study of wounds in dynamics.

3. Invasive studies: Seldinger angiography using "Philips Integris Allura" (Netherlands).

Among the patients of the study group with CAI, 2 patients underwent femoral shin shunting, 2 patients underwent hybrid reconstructive surgery (femoral-popliteal reconstruction in combination with balloon angioplasty of the tibial artery), and in 4 cases endovascular interventions on the tibial arteries. Patients with CVI underwent scleroobliteration of incapable perforators under ultrasound navigation (as a phlebosclerosant used "Ethoxysclerol" 0.1–3 %, foam was obtained by the method of Tessari (ratio air-drug 4:1).

In patients with CAI, there were wounds after necrectomies and small amputations in the foot that could not be closed with autodermoplasty.

Treatment of patients was prescribed according to the following scheme: DM compensation (transition to small insulin therapy), metabolic therapy, antibacterial, anticoagulant and angiotropic therapy, physical therapy, therapy aimed at treating osteoporosis.

In order to improve the results of treatment of wounds and ulcers of the extremities, the study patients used a combination of the following methods of local treatment: photodynamic therapy (PDT) and staged closure of tissue defects with human amniotic membrane.

At hospitalization, surgical treatment of wounds with removal of necrosis and elimination of purulent effusions with subsequent treatment with antiseptic solutions was performed. The next day in the area of the bottom and edges of the wounds remained areas of necrosis and fibrin plaque. After toilet wounds with antiseptic solutions, the wound was loosely tamponade with a gauze napkin, impregnated with photosensitizer (PS), (exposure 20 minutes). As PS we used Dimegin (disodium salt 2,7,12,18-tetramethyl-3,8-di(1-methoxyethyl)-13,17-di(2-oxycarbonyl ethyl)porphyrin). The drug is characterized by prolonged elimination from the body, which prolongs its bactericidal effect in the wound. After removal of the napkin from PS, the wound was irradiated with violet or blue light (λ 405 or 470 nm) with a photonic matrix "Color Flex" of O. M. Korobov. After stabilization of regional hemodynamic parameters and before the appearance of conditions for plastic closure of defects, bandages were performed daily using hydrogel dressings.

When granulations appeared at the bottom of the wound, the wound surface was closed with a human amniotic membrane (after treatment according to the standard surgical protocol) to prevent secondary infection, stimulate the growth of connective (granulation) tissue in the wound and create conditions for wound healing by wound contraction.

The collection, systematization of source information and visualization of the obtained results is carried out in spreadsheets Microsoft Office Excel 2007. Statistical analysis was performed using the U-test Mann-Whitney for nonparametric data, using the Yates's correction for parametric data. Intragroup analysis was performed using Wilcoxon's T-test. Statistical significance was taken as $p<0.05$.

3. Research results

Against the background of treatment, positive changes were noted in the microbial landscape of wounds. Upon admission, mainly Gy + microorganisms with an average wound colonization of 7.42×10^9 CFU were isolated. The most commonly identified staphylococci (in 8 patients) with mean colonization $(8.46\pm0.82)\times10^9$ CFU, in second place (in 6 patients) were streptococci $(7.24\pm0.84)\times10^9$ CFU and in 4 patients – gram-negative flora of E. coli and Pseudomonas aeruginosa ($7.58\pm\pm0.87\times10^9$ CFU in one observed wound infection decreased below the critical values $<10^5$, in 3 cases this required a second session of PDT.

Transcutaneous tension of O_2 up to 5–7 days of treatment in patients with CAI was 0.5–0.6 mm Hg.

The surface area of wounds in patients with obliterating lesions of the arteries of the lower extremities before treatment averaged 391.3 ± 100.42 cm^2 for 5–7 days 364.7 ± 44.21 and for 10–12 days of treatment – 4.72 ± 0.63 ($p<0.01$).

In patients with CVI after scleroobliteration of incapable perforators and PDT, the dynamics of regression of wound area was as follows: after manipulation – $16.92\pm\pm0.18$ cm^2, for 4–5 days – 10.28 ± 0.24 cm^2 (by 39.24 %, $p<0.05$), 7–10 days – 7.82 ± 0.68 3 (by 50.63 %, $p<0.01$).

In patients with mixed arterial and venous pathology in one case as the first stage was performed balloon angioplasty of the tibial arteries, the second stage was performed scleroobliteration of failed perforating veins, after which local treatment was performed by different methods. In one case, a patient with stage II Fontaine ischemia underwent conservative vasotropic therapy and scleroobliteration of perforators followed by topical treatment.

Cytological examination of smears-imprints of wounds at hospitalization revealed in 5 patients of degenerative-inflammatory type, in 6-purulent-necrotic, in 7-purulent – inflammatory type of cytograms. At 5–7 days after

PDT, the cytology of wound impressions changed: in 7 patients with inflammatory type and in 11 – with inflammatory-regenerative. Carrying out a complex of local treatment for 13–15 days changed the type of cytogram to regenerated in 16 patients.

In all cases, it was possible to achieve spontaneous epithelialization of wounds within 15 to 41 days (depending on the initial state of the wounds). The average length of stay in the hospital is 22.6±2.4 days.

Here is a clinical case.

Patient K., 68 years old, was admitted to the clinic SI "V. T. Zaitsev Institute of General and Emergency Surgery National Academy of Medicine of Ukraine" with the phenomena of ischemia of the II century, right limb and extensive trophic ulcer on the leg on the background of DM II type. He was treated for 2 months in the CDH at the place of residence. According to ultrasound and angiography - prolonged stenosis of the patella and RITA, collateral hemorrhage. According to Doppler, failed perforating veins were detected, PTPhD (recanalization 70 %). Bacterial culture from the wound – infected. S. aureus 7×10^9 CFU, cytogram type – degenerative-inflammatory.

The patient was prescribed vasotropic therapy, performed a session of PDT, followed by scleroobliteration of failed perforating veins. After two sessions of PDT, there was a decrease in wound contamination below 10^3 CFU, and improvement in wound characteristics (Fig. 1).

Fig. 1. Patient K. Wound after PDT

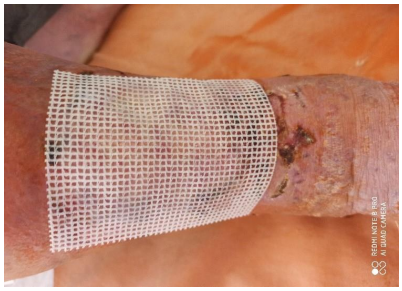
The wound was then treated with antiseptic solutions and covered with hydrogel dressings.

On day 10 of treatment, the wound surface was closed with an amniotic membrane and a "Grassolind" mesh bandage (Fig. 2).

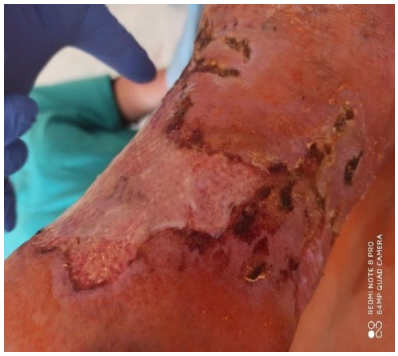
On the 12th and 15th day of treatment, repeated closure of the wound surface with an amniotic membrane was performed (Fig. 3).

The patient was discharged on the 17th day after surgery, local treatment was performed in the day hospital. The wounds healed on the 31st day of scleroobliteration of perforating veins (Fig. 4).

When using traditional methods of treatment of chronic wounds, cytological examination indicates a slow course of the wound process: on the 3rd and 6th day, no significant differences with the result are observed. Only on days 14–21 of traditional treatment there is a slight decrease in microbial contamination, increased phagocytosis and a slight increase in the content of macrophages and fibroblasts, i. e. the transition to the inflammatory type of cytograms [10].

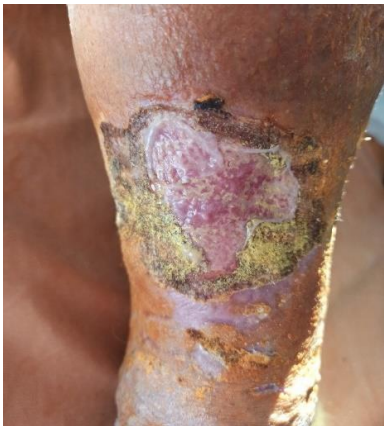


a



b

Fig. 2. Patient K., wound closure: *a* – wound closure with a mesh bandage; *b* – wound closure with amniotic membrane



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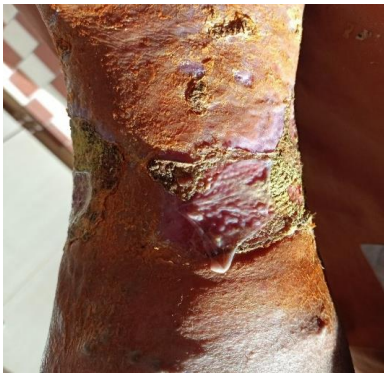
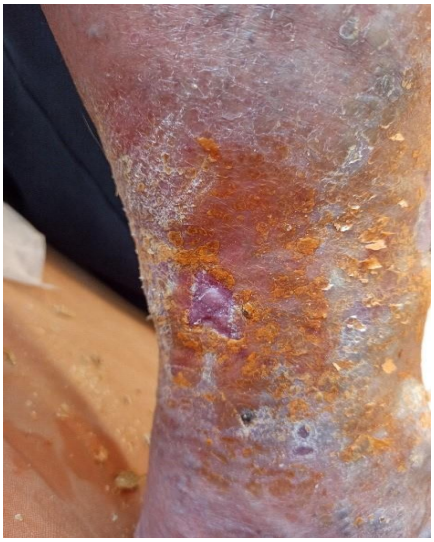


b

Fig. 3. Patient K., the dynamics of wound healing: *a* – 12th day; *b* – 15th day of treatment

a



b

Fig. 4. Patient K. Wound at the end of treatment:
a – 21st day; *b* – 31st day

The number of neutrophils in the wound smears was significantly reduced after 1–2 sessions of PDT, which may be due to the accumulation of PS in them and their subsequent destruction by light. After 3 days, the absolute number of neutrophils increases due to new cells with active phagocytic function, migrating from the vessels with granulation tissue, while increasing the composition of macrophages, including mature, actively phagocytic forms, and then fibroblasts with varying degrees of maturity. This indicates the transition from inflammatory-necrotic type to inflammatory, and then to inflammatory-regenerative and regenerative. Thus, cytological examination shows that the use of PDT promotes early cleansing of wounds from necrotic detritus and reduces the level of microbial contamination, as well as increased phagocytosis, accelerated macrophage and fibroblast response.

4. Discussion

When using PDT, the course of the wound process intensifies: on the 7th day the microbial contamination decreased or completely disappeared, the disappearance of necrotic detritus was observed, which corresponded to the data of cytograms. It should be noted that in some patients in whom the pathological granulation tissue before treatment had a weak neutrophilic response, the next after the first session of PDT was temporarily increased, which can be considered a good prognostic sign, given the role of neutrophils in wound cleansing. After 7–14 days, the number of macrophages in the tissue increased significantly, with the predominance of mature macrophages with active phagocytic function.

In general, the inflammatory phase on the background of PDT proceeds much faster and at an earlier date turns into reparative.

After application of the amniotic membrane as a wound coating, active proliferation of fibroblasts, formation and maturation on the 14th day of full-fledged granulation tissue with vertical vessels, which on the 21st day turned into fibrous-scar. At the same time there was a regeneration of the epidermis: on the 7–14th day there was a marginal growth of immature epithelium, and by the 21st day a mature epithelium was formed. The size of the wounds was reduced due to epithelialization and contraction of scar tissue. In addition, the amniotic membrane corresponds to the shortening of treatment, reduces the need for antibacterial therapy and is an alternative to autodermoplasty.

The results of treatment showed that the method of using heterografts, namely the use of the amniotic membrane, is far superior to other modern methods of treatment of chronic wounds. In particular, we managed to achieve complete closure of wounds within 3–4 weeks. Nelson R. Pinto et al. in their study used blood plasma enriched in leukocytes and platelets and achieved complete epithelialization only in the seventh week [11]. In another study by M. Sako et al. a comparison was made between the use of hydrogel, foam and hydrocolloid dressings in the treatment of diabetic foot and trophic ulcers in CVI, where complete closure of ulcers is achieved only in the eighth to twelfth week [12].

Study limitations. Unfortunately, due to insufficient funding, it seemed impossible to conduct a more detailed study of the wound process and to determine a more accurate effect of the amniotic membrane on regenerative processes.

In addition, some patients showed resistance, at the ethical level, in accepting the idea of using amniotic tissue for treatment. This affects the patient's consent to the proposed treatment tactics, however, this problem can be corrected by a clear explanatory conversation about the nature of the cover material.

Prospects for further research. It seems promising to study changes in cytokine levels and the immune response to the use of amniotic membrane in the wound.

It is also necessary to conduct a comparative analysis of the rate of mitosis and cell proliferation of the basal layer of the skin when using the amnion and without. To reduce the error and variability of the results, this study should be performed "In vitro".

5. Conclusions

The use of a heterograft, namely the amniotic membrane allows to achieve shorter healing times of chronic

wounds in patients with diabetes, healing is 2–3 times faster than other modern treatments. In turn, this reduces the economic costs of the patient and the clinic for the treatment of chronic wounds and allows able-bodied patients to return to work faster. Reducing the duration of treatment of patients also reduces the burden on medical staff and improves the quality of life of patients with diabetes, and faster wound cleansing reduces the risk of local infectious complications.

Conflicts of interest

The authors declare that they have no conflicts of interest.

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