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MODERN APPROACHES TO THE TREATMENT OF TROPHIC ULCERS VENOUS ETIOLOGY. PHOTODYNAMIC THERAPY

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ABSTRACT

Chronic venous insufficiency, which is the cause and complication of most diseases of the lower extremities, is a fundamental cause of trophic ulcers. During the last decade, some progress has been made in addressing venous trophic ulcers both theoretically and practically. The modern concept of treatment of patients with trophic ulcers of venous origin suggests a reasonable combination of the following treatment methods: local, compressive, as well as medicinal, surgical, low-invasive and additional methods (physiotherapy, photodynamic and others). The main goal of treatment is to eliminate the ulcerative defect, after which measures are taken to correct the root cause (chronic venous insufficiency) and prevent recurrence. However, the most successful treatment of patients with trophic venous ulcers is still not defined and needs further improvement. In particular, the method of photodynamic therapy using special pharmacokinetics photosensitizers deserves to be studied and its prospects for clinical use extended. The mechanism of photodynamic action is based on the ability of photosensitizers to accumulate in microbial and pathological cells. Under local light exposure, the photosensitiser becomes excited and charges oxygen associated with erythrocyte hemoglobin. Thus, in the cells under exposure, a photochemical reaction is initiated that produces singlet oxygen and its free radicals. Active oxygen forms, in turn, have a damaging effect on pathogenic flora and necrotic tissues. The main advantages of the method are relative simplicity, no risk of developing antibiotic resistance, acceleration of regenerative processes, prevention of secondary infection. Thus, photodynamic therapy allows to optimize local treatment and pre-operative preparation of patients with venous trophic ulcers non-invasively, safely and effectively.

Key words: chronic venous insufficiency, trophic ulcer, treatment, photodynamic therapy, photosensitizer.

INTRODUCTION

Chronic venous insufficiency (CVNO) is a key cause of formation and progression of trophic ulcers. Up to 70% of trophic ulcers have venous etiology, and the frequency of their occurrence in patients with HBV is about 15-20%. Such ulcers are accompanied by a painful syndrome from «moderate» to «strong», lasting until 3 months. after the wound closure, which in combination with frequent ulcer relapses can significantly reduce the health-related quality of life of patients. Trophic ulcers, which arise against the background of decompensation of HBV, often lead to loss of ability to work and disability of patients [1, 2].

Pathogenicity of trophic ulcers in chronic venous failure

The development of trophic changes in HBV is based on phlebohypertension, and the direct cause of formation of ulcerative defects are deep microcirculatory disorders, the degree of which directly depends on the severity of the HBV. Arterial and deep superficial vein hypertension in patients with venous trophic ulcers develops due to retrograde blood flow when there is a relative or absolute insufficiency of valves of the subcutaneous, deep and perforated veins (VSD) of the lower extremities. The widening of the veins against the background of phlebohypertensis leads to an aggravation of valve dysfunction and causes the formation of a cycle macro-circulatory disorders. They secrete transmuscular and extramuscular PT, the latter being localized in the Achilles region of the cellular window, most vulnerable to the development of valve insufficiency, which causes the development of trophic disorders of soft tissues in this «classical» zone [3].

The implementation of hemodynamic disorders, in particular phlebohypertension, is carried out at the level of microcirculation, i.e. macro circulatory disturbances are transferred to microcirculation [4]. The result is microthromba, local hypoxia and then necrosis [5]. Activated endoelectrolytes activate the formation of inflammatory mediators and cytokines, support the secretion of endothelial vascular growth factor (VEGF) and other components inducing vein wall hypertrophy. The most common theory of formation of venous trophic ulcers is the concept of «leukocyte trap», according to which skin damage is caused by the extraction of blood cell elements into skin interstitiations. The outcome of inflammatory response is development of manifestations on the side of the skin: hyperpigmentation, eczematous dermatitis, liposarmasleriasis, exudation [6].

Phlebohypertension and occlusion of the venous drain lead to inclusion of arteriovenous shunts in the blood circulation system: arterial blood, enriched with oxygen and energy substrate, is directed into the bypass microcirculator, immediately released into the venous system. The discovery of precapillary shunts

is accompanied by hypotension in the arterial and hypertension in the venous parts of the capillaries, which severely disrupts the transport of oxygen and nutrients and provokes necrosis [7].

Treatment of trophic ulcers in chronic venous insufficiency

The current concept of treating patients with trophic ulcers of venous etiology involves a sensible selection and combination of the following treatment methods [8]:

- local, i.e. compression
- Medicated
- Surgical
- Low-impact
- additional (physiotherapy, photodynamic and others)

Local and compression therapy is a fundamental method of treating venous ulcers. Compression therapy creates an additional «carcass» for the veins, preventing their stretching, reduces pathological venous capacity, improves the work of the venous valves, increases the fluid resorption from tissues, optimizes lymph drainage, reducing tissue ooze, accelerates venous flow through the deep veins, preventing them from thrombosis [9]. It may be the only and sufficient remedy for a trophic ulcer, so it is recommended to be administered to all patients at all stages of therapy [10]. The 2012 Cochrane Review confirmed that compression increases healing rates, with multi-component bandage systems being more effective than single-component or single-layer bandages. There is not enough evidence for the efficacy of compression knitwear in preventing recurrence of trophic ulcers [11].

Pharmacological therapy involves the use of drugs (PS) with different spectrum of pharmacological action. The first line of agents are phlebotonics and phleboprotectors (Детralex®, Venarus®, Flevodia®) containing diosmin and gesperidine bioflavonoids. Several large randomized trials have proven their effectiveness in treating primary venous ulcers as a complement to compression and local therapy [12, 13], which is also reflected in international clinical recommendations with an 1V level of evidence. PL can be used in the treatment of trophic ulcers by affecting pathogenetic mechanisms, or as a symptomatic treatment, but they are not standard of care [14].

Surgical treatment. To date, a significant number of surgical treatment techniques have been developed, such as: epifascial PW-bandage by mini-phlebectomy [15] or coquettic, endoscopic perforation surgery (SEPS) [16].

Minimally invasive treatment. In modern phlebology, along with traditional surgical procedures, endovenous vein delineation methods are also used, which

include various variants of sclerosis (in particular, foam sclerotherapy [17]), radio-frequency coagulation, endovenous laser imaging (EVLO). Advantages of these techniques - low traumatic, possibility of execution in outpatient conditions, efficiency and favorable aesthetic result. EVOL of subdermal trunks and PV in combination with microfoam sclerotherapy of subdermal appendages is a low-risk intervention that can eliminate pathological reflux without post-operative complications. However, there are no randomized studies evaluating the effectiveness of standard treatment and EVLO in patients with venous ulcers.

ADDITIONAL TREATMENT

Electroscopic stimulation has already proven to be effective as a method that increases linear and volumetric venous blood flow, reduces venoseptic symptoms and chronic venous edema, and also the prevention of phlebothromycosis and post-thrombotic disease [18]. As a treatment method for C3 CBR, it is included in the European and international guidelines.

Magnetic therapy. The application of magnetic therapy allows to achieve cleaning of ulcerative surface, significantly reduce pronounced microcirculatory disorders (there is a reduction in microtubules, erythrocyte slagia, aggregation of platelets, vascularitis). There is an increase in the neutrophil and macrophage phagocyte activity towards bacteria, a decrease in the inflammatory response of tissues. The ability of magnetotherapy to reduce edema in HBV is particularly important [19].

Vacuum therapy. Studies show that the application of vacuum therapy in the treatment of patients with trophic ulcers accelerates wound cleansing processes, stimulates the formation and maturation granulating tissue, reduces the frequency of postoperative complications [20]. The 2015 Cochrane review also reports that there are currently not enough randomized controlled vacuum therapy trials for treating trophic ulcers of the lower extremities [21].

Hyperbaric oxygenation (HBG). It is suggested that HBG improves the oxygen supply of wounds and therefore their healing [22, 23]. However, the 2015 Cochrane review reports that HBG has significantly improved healing of ulcers in the short term only, and existing studies on its effectiveness have a number of methodological shortcomings, which makes their results questionable [24].

Photodynamic therapy (PDT) is a relatively new but promising method of treatment for HBV. This method is based on the application of special PL - photosensitizers (FC), which are characterized by specific sensitivity to light, in combination

with low-intensity laser radiation with wavelength corresponding to the absorption capacity of HF. The mechanism of the photodynamic effect is based on

the ability of CF to accumulate in microbial and pathological cells. Under local light exposure, HF becomes excited and charges the oxygen associated with erythrocyte hemoglobin. Thus, in the cells under exposure, a photochemical reaction is initiated that produces singlet oxygen and its free radicals. Active oxygen forms (AFCs), in turn, have a damaging effect on pathogenic flora and necrotic tissues [25].

PHOTODYNAMIC THERAPY FOR TROPHIC VENOUS ULCERS

The FDT method was originally used in oncology because, besides direct phototoxic effects on microorganisms and tissues, it also has a stimulating effect on the production of tumor necrosis factor, increases leukocyte and lymphocyte activity [26]. This fact led to the development of the TDF method for non-cancerous diseases, in particular for the purpose of antibacterial effect for the treatment of fused, long-lasting wounds and trophic ulcers.

The excessive use of local and systemic antibiotics now contributes to the high prevalence of multi-drug-resistant microorganisms in patients with trophic ulcers. Unlike antibiotics, the antimicrobial effect of TDF does not disappear over time, i.e. pathogenic microorganisms do not develop resistance to TDF [27].

Photodynamic inactivation involves three independently non-toxic elements: HF, light of appropriate wavelength and molecular oxygen, which lead to the generation of AFCs responsible for inactivation of microorganisms, i.e. present in bioplastic form in chronic wounds [28].

Among the several molecules used as SF, porphyrinoids show suitable features to effectively achieve these goals. The ability of these macrocycles to generate AFC contributes significantly to the regenerative process. AFC are responsible for preventing the development of infections by inactivating microorganisms such as bacteria, and for stimulating cell proliferation by activating stem cells that regulate inflammatory factors and remodeling collagen. CF can act alone or in combination with several materials such as polymers, hydrogels, nanotubes or organometallic frameworks, maintaining both the efficiency of microbial photoinactivation and regeneration processes [29].

The bactericidal effect of the DFT method is limited by the laser irradiation zone of sensitized tissues, which allows to avoid systemic adverse reactions characteristic for the application of antibacterial and antiseptic drugs in local DFT. In addition, limited penetration of antibacterial L-s into infected sites, which is aggravated by the ischaemia, reduces the effectiveness of traditional treatment methods [30].

In case of CFM with formation of trophic ulcers in combination with contraindications to the operative treatment, PDM should be applied using

different techniques for applying laser effects to the affected tissues: superficial, intra-uterine, Intra-urinary, endolimbic and mixed [31].

The use of TDF has recently been of great interest and prospects in the treatment of septic wounds and trophic ulcers. In this context, TDF can be a useful «tool» with the following advantages [32-35]:

• Quick and effective action;

• Broad spectrum of antimicrobial activity, including multi-drug resistant strains;

• No resistance development;

• No influence on normal tissues or bacterial flora outside the site of the infection;

• No systemic absorption of PS.

The injury-causing process requires the release of certain cytokines, especially IL-10, which stimulates the absorption of tissue inflammation as well as growth factors (VEGF, FGF, PDGF and TGF-b), which promote cell proliferation and the synthesis of extracellular matrix to repair damaged tissue.

There is evidence in the modern medical literature of the positive effect of laser biostimulation on healing wounds in cell cultures, in animal models and clinical settings. These effects include local blood circulation enhancement, stimulation of cell proliferation, enhancement of cellular and subcellular processes required for the formation of Type I and III collagen, and enhanced synthesis of ATP [36].

One such study presents data on the success of antimicrobial PDT with 5-aminolevulinic acid photodynamic therapy (ALA-PDT) in patients with trophic ulcers resistant to other therapies. Healing occurred after 1-3 sessions, and the recurrence was no more than 29 months. After ALA-PDT, the microflora-separated lesions had become negative. In vitro ALA-PDT also inactivated all bacteria released from patients. Results show that in addition to bactericidal effects, ALA-PDT also alters the wound microenvironment [39]. Similarities

Data were also provided by A. Kawczyk-Krupka et al. [40]. In addition, ALA-PDT influenced the state of macrophages polarization by activating and modifying macrophages from phenotype M1 to M2 [41].

Another study reported that photodynamic exposure is associated with increased IL-10 levels and suppression of pro-inflammatory cytokines [42]. A recent study evaluating the release of cytokines by keratocytes after in vitro photodynamic exposure has shown a decrease in IL-6 and IL-8 concentrations within 5 hours of PS application [43]. The effect of FGF on in vitro release of

growth factors in keratotic cultures has also been studied earlier: elevated FGF concentrations were observed for 5 hours after therapy [44].

V. Grandi, S. Bacci et al. [45] in their study performed a 4mm perforation biopsy of the wound bed of trophic ulcer before applying 20% ALA gel and then repeated the sampling one hour after the first irradiation by TFD. There was a significant and progressive reduction in the average number of wounds immediately after three ALA-PDT sessions. Immunofluorescent biopsy of biopsies showed changes in all test samples after treatment compared to the samples before therapy, namely an increase in plasmocytoid dendritic cells; MHC-II expression, TNF alpha positive expression of fat cells, Expression of TGF-beta and CD4+/CD25+ Treg cells. The increase in TGF-beta was statistically correlated with the decrease in average wound size.

Another study by V. Grandi [46] included 19 patients with trophic ulcers associated with HBV. Skin samples were taken from the wound bed before and after ALA-PDT irradiation. All samples were anonymized and analyzed by immunohistochemical method. After completion of ALA-PDT, the fat cells showed an increase in the degradation index and expression of NGF (nerve growth factor) and VIP (vasoactive intestinal peptide). Among all the tested neuronal mediators, all but SP (substance P) showed increased cellular expression after ALA-PDT therapy, which is evidence that ALA-PDT induces a rapid set of mast cells around dermal fibers in trophic ulcers. This discovery is also associated with increased expression of multiple peripheral neuropeptides. ALA-PDT can contribute to the healing of chronic venous ulcers through stimulation of «calm» peripheral nerves, possibly after the release of inflammatory molecules by degrading fat cells.

In one study [40] authors used multisession ALA-PDT for treating ulcers, mainly due to HBV, with experimental evaluation of the effectiveness of red light compared to red light + ALA, antibacterial activity ALA-PDT and ALA-PDT activity compared to standard bandage used in the study. All patients included in the study had multiple and/or large ulcers (area > 20 cm2). After formal informed consent of patients, multiple ulcers were grouped and treated with: 1) standard dressing only; 2) standard dressing and weekly ALA-PDT and 3) standard dressing and weekly exposure to red light. The treatment of ALA-PDT consisted of applying 10% ALA in polyethylene glycol ointment for occlusion for 24 h followed by exposure to dired red light at 630 nm, radiation 160 MWe at 50 mm for 8 min, providing 75 W/cm2. Microbiological samples were taken from all ulcers for primary isolation of gram-negative bacteria, Gram-positive cocci and mycelium before ALA or dressing, after 24 hours of ALA occlusion or dressing

and after exposure to red light. The study found that multisectional ALA-PDT heals all treated ulcers twice as fast as standard dressing on the same patient; red light exposure alone does not contribute to healing wounds and ALA-PDTPDT does not have any direct antibacterial activity. These in vivo results demonstrate the beneficial activity of ALA-PDT in wound healing, although the underlying biological mechanisms are not yet fully understood.

Promising study conducted by X. Xu, L. Lin et al. [47] on mice to introduce a new automatic protocol for quantitative vasoconstriction of blood vessels in the DSWC model, which focused on tracking blood vessel pixels in images before V-PDT (vascular targeting photodynamic therapy) that disappear after V-PDT. There was a significant difference in vasoconstriction between the control and V-PDT group. The results open new possibilities in the treatment of HBV.

One study [48] analysed the treatment outcomes of 126 patients with trophic ulcers of venous lower limbs: patients in group 1 (77) underwent PDM, and patients in group 2 (49) received standard treatment. Radachlorin - gel, which was applied to the surface of the ulcer in a film form, was used as CF. After 30 minutes, the ulcer defect was irradiated in the visible range 635, 660, 675 nm at a maximum power of 3 W. Patients in the 2nd group were given oil bandages and a chlorhexidine solution as local therapy. Further surgical intervention in the volume of «classical» phlebectomy and free autodermoplasty with splinter flap was performed on 75 patients of group 1 and 46 patients of group 2. The evaluation of the distant treatment results was carried out in a period of 3 months to 3 years. The results of this study showed that PDT as a conservative physiotherapy method allowed to reduce the pre-operation period by 3 times (the time for performing surgical interventions was 5.2 0.4 days). Also, patients of the 1st group had a significantly higher success rate of autoderma transplantation (75.4% of patients of the 1st group versus 46.8% of patients of the 2nd group).

It was also noted that FDT therapy has a pronounced antibacterial effect and improves the processes of epithelialization. Study conducted by S. Katorkin et al. [49] in patients with C6 clinical class CWHC showed that the patients who were administered DFP had a stable decrease in growth of microbial flora and the level of microbial prevalence of ulcerative defects. In addition, 73% of cases already 4 days after the beginning of treatment were recorded «inflammatory-regenerator» cytopgrams. The patient was treated with a CPR.

Antibacterial effect is also confirmed by another study [50] in which two groups of patients with trophic leg ulcers were compared: the control group received traditional complex treatment using standard principles of local therapy, a

primary - Local treatment with complex technology: FDT and subsequent local transplantation of the MDC

CWT. As a result of treatment, the overall microbial count decreased to an etiologically insignificant level (<103 CHD/ml) in KG against the background at 10-12 days of observation, whereas in the experimental group with local PWD within 5 days - already at 4-5 days. Regardless of the size of the trophic ulcer. Patients in the 2nd group were given oil bandages and a chlorhexidine solution as local therapy. Further surgical intervention in the volume of «classical» phlebectomy and free autodermoplasty with splinter flap was performed on 75 patients of group 1 and 46 patients of group 2. The evaluation of the distant treatment results was carried out in a period of 3 months to 3 years. The results of this study showed that PDT as a conservative physiotherapy method allowed to reduce the pre-operation period by 3 times (the time for performing surgical interventions was 5.2 0.4 days). Also, patients of the 1st group had a significantly higher success rate of autoderma transplantation (75.4% of patients of the 1st group versus 46.8% of patients of the 2nd group).

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CWT. As a result of treatment, the overall microbial count decreased to an etiologically insignificant level (<103 CHD/ml) in KG against the background at 10-12 days of observation, whereas in the experimental group with local PWD within 5 days - already at 4-5 days. Regardless of the size of the trophic ulcer. Positive impact of PDT on skin autograft in autologous plastic surgery also confirmed repeatedly [51]: 50 patients aged 18 to 72 years with fused post-traumatic wounds and trophic ulcers of the lower limbs of different etiology were examined. For them FD was applied by the machine «Rodionic-1» with FC Chlorophyllylpt. The analysis showed that as early as possible surgical treatment of the wound and subsequent DFP allow to create the most favorable conditions

for the insertion of a skin transplant due to the pronounced antibacterial effect, Improvement of the microvascular system of tissues to be treated, stimulation of macrophage reaction, activation of granulation processes. This accelerates the preparation of patients for skin transplantation and ensures a higher level of tissue adhesion.

Y. Ivanova, E. Klimova et al. [52] conducted a study to improve the treatment of trophic ulcers in patients with HCV by combining techniques such as artificial wound dressings, growth factors, platelet-rich, and phototherapy. The study showed that the use of a treatment complex consisting of phototherapy, foaming of incompetent perforating veins under ultrasound navigation and closure of the wound with synthetic plaque with a thrombocytic growth factor, is an extremely effective stimulant for the development of granulating tissue and spontaneous wound epithelialization.

The study conducted by I. Kryvoruchko, O. Zarudnyi et al. [53] included 24 patients with venous ulcers in a context of post-thrombotic disease and aged between 31 and 79 years. The comparison group included 14 patients who were treated with standard treatment (venotonic drugs, elastic compression, local application of multicomponent ointments depending on the wound phase). The main group included 10 patients who were applied to the developed TFD technique. In the treatment of patients, a Pobova photon matrix «Barva Flex», spectral range 700-630 nm, corresponding to red light was used. Levutin gel was used (6% of the 5-aminolevulinic acid phosphate gel, which is a natural precursor of endogenous protoporphyrin IX). The transition of the wound process to the second stage in the comparison group was long, 50% of patients had their epithelialization not completed until the 45th day of treatment. In the main group, under the proposed treatment, the time of occurrence of granulations was reduced, as well as the filling of the wound with mature granulating tissue, and epithelialization was accelerated by 29.8% compared to standard therapy.

The crucial role in the effectiveness of TDF for trophic ulcers is played by the correct selection of the appropriate SF and its dose, as well as a clearly defined range of electron absorption spectra and other light parameters such as flux rate and light doses [28]. The healing rate after a FDT session is directly dependent on the initial parameters. With a wound area of 150 to 600 mm2, the rate of reduction of the wound surface is maximum at 14 and 30 days. During this period, the wound is reduced by 8.7 and 7.4 times respectively. Full healing occurs after 2 months. FDT allows to achieve adequate, highly effective therapy, reduces the healing time of festering post-operative wounds, improves quality of life of patients [54, 55].

Conclusion

The development and implementation of effective methods for the treatment of trophic ulcers in HBV remains one of the most pressing problems of modern fbology. In this aspect, the scientific and practical interest is TDF, which allows to optimize local treatment and pre-operative preparation of patients with venous trophic ulcers non-invasively, safely and effectively. Based on the beneficial interaction between light, photosensitive (LH) and oxygen, FDT has gained popularity among various therapies. Better cosmetic results, minimal functional impairment, good patient tolerance, minimization of systemic toxicity are the main advantages of TDF that certainly make this method promising and relevant [56].

The systematic review of randomized trials Cochrane 2017 [57] has shown that TDF compared to its absence in the treatment strategy or with a placebo can increase the proportion of fully healed ulcerative defects, as well as reduce the size of wounds, However, there is no convincing evidence that TFD improves the quality of life. Due to the small sample size and methodological shortcomings in the original tests, the level of evidence was low. Therefore, further detailed study of the effectiveness of TDF in trophic ulcers is certainly necessary.

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