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The Study Of The Effectiveness Of The Drug Combination Of Collagen And Platelet-Rich Plasma For The Regional Treatment Of Venous Ulcers.

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ABSTRACT

To assess the clinical effectiveness of the drug combination of collagen and platelet-rich plasma for the topical treatment of trophic ulcers the comparative study controlled parallel groups of 85 patients with chronic venous insufficiency of the 6th international stage according to the CEAP classification. Patients were randomly divided into the main group, which included patients to whom for local treatment of trophic ulcers we used a combination of drugs of collagen and platelet-rich plasma and 3 control groups: in the first we used modern dressings the complex treatment of patients, in the second only collagen preparations were used in the integrated topical therapy, the third control group included patients who used platelet-rich plasma. The healing process was evaluated by measuring the ulcer, the condition of the skin around wounds, bacteriological examination of wound discharge, cytological and pathological-histological studies of wound tissues, instrumental methods of research. Comprehensive clinical and laboratory study of the effectiveness of various methods aimed at the stimulation of reparative processes in trophic ulcers showed that the application of the drug combination of collagen and platelet-rich plasma significantly accelerates the epithelization of the wound surface, effectively stimulates granulation, significantly reduces the negative sensations in the wound.

Keywords: venous ulcers, drugs of collagen, platelet-rich plasma.

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RELEVANCE

Trophic ulcers is a complex medical problem, the relevance of which despite its long history is constantly increasing [1]. Serious damage to the quality of life, high disability level, the significant costs of treatment determine the social significance of the diseases accompanied by the development of ulcers [2].

In conditions of impaired nutrition the synthesis of tissue elements is slowed down in chronic wounds, the intercellular and cell-matrix interactions are altered [3]. The understanding of these features creates the fundamental preconditions for the development of advanced methods of stimulation of reparative processes in wounds [4, 5, 6].

The purpose of the study: to evaluate the effectiveness of different methods of stimulation of regeneration in the healing of nonhealing wounds.

MATERIALS AND METHODS

The study included 85 patients with varicose disease of lower extremities, 6-stage CVI, in accordance with the international classification of CEAP. 42 patients were of working age — to 60 years old. The study was conducted in the offices of outpatient and purulent surgery of Voronezh State Regional Clinical Hospital №1.

The area of the wounds did not exceed 20cm², the mechanisms of contraction of the wound edge and islet regeneration were depleted.

For the purpose of studying the clinical effectiveness of the use of drug combination of collagen and platelet-rich plasma for the topical treatment of small and medium sized trophic ulcers the comparative study controlled parallel groups. Patients were randomly divided into 1 main and 3 control group.

The main group. The main group included patients to whom for local treatment of trophic ulcers of small and medium size we used a combination of drugs of collagen and platelet-rich plasma.

The main group included 26 patients with venous trophic ulcers of the lower extremities in II stage of wound process. Among them there were 22 women and 4 men, mean age was 63,2±9.4 years. The period of existence of trophic ulcers varied from 5 months to 14 years, an average of 8.5±6.4 years. The duration of unsuccessful treatment amounted to an average of 0.2±1.2 years (from 2 months to 1.5 years). The area of venous trophic ulcers was 16,2±4,8 cm² (from 10.0 to 20.5 cm²). 23 patients had the ulcer located on one of the lower limbs, 3- on both legs. 19 patients has single ulcers, 7 - - multiple. Localization of venous trophic ulcers: the front surface of the lower third of the leg – 4 patients, the medial surface of the lower third of the leg, - 13 patients, the lateral surface of the lower third of the leg – 4 patients, 5 patients has ulcers located on prednimustine surface of the middle third of the leg.

At the first dressing the bottom of the wound of all patients in this group was infiltrated with platelet-rich plasma, and the surface of the wound was closed with a membrane consisting of collagen. We used a medicine made on the basis of highly purified soluble collagen of cattle skin. The method of obtaining allows you to save a triple-helical structure of the fiber, but it gives a high degree of purification from the ballast substances. As close as possible to human collagen it is a matrix for guided tissue regeneration: when the implant is associates with wound fibroblasts, blood and lymph vessels, nerve fibers from the surrounding healthy tissue, penetrating into collagen lattice, distributes strictly on it. Thus a transition matrix is being created that stimulates the body's immune system, improves the transfer of growth factors, activates granulocytes, macrophages, fibroblasts, increases the migration of the latter and proliferation of epithelial cells. In the process of healing biomaterial is directly is replaced by its own connective tissue, excluded the disorderly growth of granulation tissue is excluded as a response of the organism to rapid closure of the wound.

The top of the collagen membrane was covered with the wound bandage or sterile gauze pad treated with 0.9% NaCl solution. The dressing was secured to the healthy skin surrounding the lesion, and was watered when became dry. Further on the patient had bandaging every five or seven days until the complete healing of the wound.

The 1st control group. In the first control group in complex treatment of patients the modern dressings were locally used, the choice of them was in strict accordance with the modern concept of treatment of chronic wounds. Objectives of treatment at the stages of proliferation and epithelialization are the creation of optimal conditions for regeneration, mechanical protection of immature connective tissue, acceleration of the formation and retraction of the connective tissue scar. The basis of modern local treatment are the means for healing in a wet environment, that is, creating and maintaining conditions close to physiological ones. Polyurethane foam dressings, hydrogels, alginates were used as well as, water-solubility hydrocolloids-kolloidnye bandage, a change of which occurred every 2-4 days, in some cases every 7 days. It should be noted that to none of the patients the technique of wound healing in a moist environment had not been previously used. The treatment was carried out on the background of compression therapy, which included wearing the elastic knit of the second degree of compression.

The first control group included 19 patients (13 women and 6 men) with venous trophic ulcers of the lower extremities in II stage of wound process. The average age of patients was 65.3 ± 7.2 years. The period of existence of trophic ulcers varied from 2 months to 11 years, an average of 5.5 ± 6.3 . The duration of unsuccessful treatment (the period of time during which the ulcer was not closed even once) was in average 1.7 ± 1.3 years (from 2 months to 3 years). The area of venous ulcers was 10.3 ± 5.8 cm² (3.0 to 16.5 cm²). 14 patients had the ulcers located on one of the lower limbs, 5- on both legs. 15 patients had single ulcers, multiple – 4. Localization of venous ulcers: the front surface of the lower third of the leg – 4 patients, the medial surface of the lower third of the leg – 8 patients, 7 patients had ulcers located on prednimustine surface of the leg.

The 2nd control group. For patients of the second control group in an integrated topical therapy only drugs of collagen were used. The latest in the form of membranes, gels are used as a factor of stimulation of tissue regeneration. We used the preparation made on the basis of highly purified soluble collagen of cattle skin.

The second control group consisted of 22 patients with venous trophic ulcers of the lower extremities in II stage of wound process. There were 19 women and 3 men in the group, mean age was 76.8 ± 8.4 years. The period of existence of trophic ulcers varied from 8 months to 17 years, on average 6.5 ± 6.1 . The duration of unsuccessful treatment (the period of time during which the ulcer is not closed even once) amounted to an average of 2.2 ± 1.1 years (from 2 months to 3 years). The area of trophic ulcers - 18.1 ± 1.8 cm² (from 5.0 to 18.5 cm²). 15 patients had the ulcer located on one of the lower legs, 7 on both legs. 13 patients had single ulcers, 9 - multiple. Localization of venous ulcers: the front surface of the lower third of the leg – 4 patients, the medial surface of the lower third of the leg - 10 patients, 7 patients had ulcers located on prednimustine surface of the leg, in one case, on the lateral side of the leg.

The drug was applied to the wounds in the form of a membrane. Before using collagen membrane was soaked in 0.9% NaCl solution and cut in the shape of the wound. The prepared membrane was laid on the wound surface and stitched, so it could not shift. The indispensable condition: collagen membrane must be fully fit to the bottom of the defect. The top of the wound was covered with material that provides healing in a moist environment (hydrocolloid and water-solubility-kolloidnye bandage, sterile gauze pad treated with 0.9% NaCl solution). The dressing was secured to the healthy skin surrounding the damaged one, was changed or watered as getting dry. Further on, the patient was being bandaged every five - seven days until complete healing of the wound.

The 3rd control group. In complex treatment of patients from the third control group platelet-rich plasma was used for the local treatment.

This group included 18 patients with venous trophic ulcers of the lower extremities. The condition of the wounds corresponded to the II phase of wound process. All the patients were women, whose average age was 51.5 ± 6.2 years. The period of existence of trophic ulcers varied from 3 months to 9 years, at an average of 7.5 ± 6.3 . The period of time during which the ulcer was not closed at once, amounted to an average of 1.4 ± 1.1 years (from 2 months to 2,5 years). The area of venous ulcers was 17.2 ± 2.8 cm² (from 1,0 to 20,5 cm²). All the patients had ulcers were located on one lower limb. 15 patients had single ulcers, 3 – multiple. Localization of venous ulcers: the front surface of the lower third of the leg -5 of patients, the

medial surface of the lower third of the leg – 10 patients, 3 patients had ulcers were located on prednimustine surface of the leg.

The results of using different methods were evaluated on the 7th, 14th, 30th and 60th days.

METHODS OF CLINICAL RESEARCH

While inspecting the venous trophic ulcers took into account the in number, location, depth, size and form. The localization, appearance of the wound allowed us to hazard a conjecture about its nature. We payed attention to the features of discharge - smell, consistency, colour.

To measure the area of trophic ulcers we used vector-raster redactron Spotlight Pro 10 (developer CSoft), after photographing the wound at a given scale beforehand.

Much attention was payed to the condition of the skin around the ulcer – pigmentation, motility, thickness, sensitivity, presence of indurative cellulite, perifocal dermatitis, pyoderma, eczema, erysipelas, secondary microbial lesions of the surrounding skin. Regardless of the stage of the wound process the bacteriological examination of wound discharge was carried out: the definition of microorganisms, more often with the help of diagnostic and differential chromogenic media; the definition of sensitivity to antibacterial preparations, as a rule, was carried out with the help of disk diffusion method. Identification of the pathogen and receiving the antibiogram made it possible to conduct adequate General and local antibacterial therapy of trophic ulcers, complicated by inflammatory processes.

Stage and dynamics of the wound process were evaluated by means of cytological examination of smears, painted by the method Romanovsky-Gimsa and by Gram (to detect bacteria).

Pathological-histological examination of tissue of trophic ulcers was conducted by specialists of BUZ VO "Voronezh regional pathologoanatomic Bureau".

In the diagnosis of diseases, leading to the formation of trophic ulcers of the lower limbs was used a number of additional surveys were used.

Among the instrumental methods of research readings there were used: ultrasonic angioscanning (USAS), Doppler ultrasound (Doppler ultrasound) on the apparatus VOLUSON E, Angiodin, ultrasound of soft tissues using ultrasound scanners, LOGIC 7, VIVID I, VIVID E, PRO FOCUS, computer and magnetic resonance tomography multisetosum CT scanner the Aquilion 64 manufactured by Toshiba and high field magnetic resonance tomograph Signa HDx 1.5 T manufactured by General Electric, Holter blood pressure monitoring, transcutaneous determination of oxygen tension in tissues.

For a quantitative substantiation of the research results the statistical methods of data processing were used. The results are shown in the digital data in accordance with the International SI system. The differences were considered significant at value $p \leq 0.05$. During the registration, processing and analysis of digital material we used the package of applied computer programs of MS Excel 11.8169.82173 TM SP3 (Microsoft Company) and MS Word for Windons, Statistic.

RESULTS AND THEIR DISCUSSION

In the main group, in which for local therapy of patients we used a range of methods aimed at stimulation of the reparative processes - the combination of preparations of collagen and platelet-rich plasma, a moist environment was maintained in the wound. When describing the subjective feelings 23 patients reported of having no discomfort (18 the loss of pain in the wound, 5 patients did not notice the change for the worse). 1 patient complained of the appearance of mild stinging in the wound, 1 patient after 3 days felt pulling pain. 21 patients after the bandage removing had the skin around the wound without signs of inflammation, the collagen membrane was swollen, loose, tightly stuck to the surface of the wound. 4 patients had the membrane partially lysed and turned into a gel-like mass, the membrane fragments remained on the wound. 1 patient, who said about nagging pains, after removal of the dressing marked maceration of the skin with areas of excoriation, there were no signs of pronounced inflammation, the membrane was lying on the wound. The tactics of the wound conducting remained the same - the

wounds are covered with sterile gauze moistened with sterile 0.9% NaCl solution. On the 14th patients did not mark any dramatic changes in their sensations of the wound. 19 patients had the membrane tightly stuck to the surface of the wound, the skin around it was not changed. 4 patients had the membrane fragments remained in the wound, the latter was granularizing, epithelializing. In 3 cases the membrane was completely lysed, the wound area decreased by an average of 3,9cm², the bottom - with bright juicy granulations, the roller of boundary epithelization expressed was. After a month of using a range of methods of stimulation of reparative processes all patients noted positive dynamics. In treatment of 15 (58%) patients of this group we achieved complete cicatrization of the ulcer, 8 had the area of trophic ulcers decreased on average by 9,6 cm² (60%) at the expense of the regional and central epithelialization, 3 patients had the wound area decreased on average by 4,8 cm² (30%)(p<0,05) due to the boundary epithelization. By the end of the 2nd month of treatment, the complete closure of the ulcer was achieved in cases with 3 more patients, the area of ulcers of 4 patients decreased by 12,9 cm² (80%)(p<0,05), 3 patients (10%) did not have significant dynamics in the area and the state of wounds, granulation is sluggish, epithelialization is slow.

In the first control group in the complex treatment of patients we used modern dressings. On the 7th day from the beginning of the observation all patients reported about the decrease of pain, burning sensation in the wound area, painless dressings. While having an objective assessment of all patients perifocal edema and hyperemia were not marked, the appearance of the wound corresponded to the II phase of wound process, granulation and epithelialization edge appeared. On the 14th day of the treatment the area of trophic ulcers decreased on average by 2,43 cm² (p<0,05) due to the boundary epithelization. By the 30th day of treatment, the area of ulcers of patients of the group decreased by an average of 6,04 cm²(p<0,05). By the end of the 1st month of treatment a complete scarring was noted in case with 1 patient, 5(26%) patients had ulcer defects twice decreased. The wounds of all patients granulated and actively epithelized. By the end of the 2nd month of the treatment the area of ulcers of patients of the main group decreased by an average of 8,5 cm². Complete cicatrization was achieved in treatment of 3 patients (15,6%), in 6 (31%) cases ulcer defects decreased 2 times, in 1 case - 4 times. All patients' wounds granulated and actively epithelized.

In the second control group in an integrated topical therapy we used collagen preparations. On the 7th day when describing the subjective feelings the 13 patients noted a decrease of pain in the wound, 6 - did not notice any changes in their sensations, 3 patients complained of occasional slight burning sensation in the wound. 21 patients after the bandage was removed had the skin around the wound without signs of inflammation, the collagen membrane was swollen, loose, tightly stuck to the surface of the wound. 1 patient had the membrane which was partially lysed and turned into a gel-like mass, the membrane fragments remained in the wound. The tactics of the wound conducting remained the same – the moist environment was maintained in the wound. On the 14th day the subjective feelings on the part of the wound did not changed. 20 patients had the membrane tightly stuck to the surface of the wound, the skin around it was not changed. In case of 2 patients, the membrane fragments remained in the wound, the last was granulating, epithelializing. After a month of using collagen drugs all patients noted positive dynamics. In treatment of 10 (45%) patients in this group we achieved complete cicatrization of the ulcer, in 8 cases the area of trophic ulcers decreased on average 9,5 cm² (50%) at the expense of the regional and central epithelialization, 4 patients had the wound area decreased by an average of 3,7cm² (21%) due to the boundary epithelization. By the end of the 2nd month of treatment, the complete closure of the ulcer was achieved in cases with 5 more patients, the area of ulcers of 6 patients decreased by 11,8 cm²(65%), in 1 case the significant dynamics in the area and the state of wounds is not marked, granulation is sluggish, epithelialization is slow.

In the third control group, in complex topical therapy we used platelet-rich plasma, on the 7th day all patients noted a decrease of pain, the feeling of heavy legs, swelling, pain from the wounds, the cramps in the calf muscles worried the patients less. While bandaging we observed the appearance of bright juicy granulations, filling almost all the bottom of the wound, the expressed roller of boundary epithelialization was formed. To 14 days of treatment, the area of trophic ulcers of 14 patients decreased by 2,3 cm²(p<0,05) due to the boundary epithelization, the bottom of the wounds was made with juicy red granulation tissue. 3 patients marked increase in the exudation from the wound and measures to protect the skin around ulcers were taken - absorbent wound dressing was used, the wounds are still clean, are actively granulating, but the depth and area of the wound did not change. After a month from starting the

treatment the area of ulcers of 14 (78%) patients in this group decreased by an average of 5,04 cm²(p<0,05) due to the parts of boundary epithelialization, 3 patients had the wounds which were fully closed, in 1 case the appearance, depth, and wound area did not change. By the end of the 2nd month of treatment in case with 1 patient we achieved complete cicatrization of the area of ulcers, 12 patients declined on 10,5 cm² (p<0,05). The ulcerative defects of the skin of the lower extremities of 1 patient were clean, they actively granulated, marginal epithelialization was insignificant.

INSIGHTS

Comprehensive clinical and laboratory study of the effectiveness of various methods aimed at the stimulation of reparative processes in trophic ulcers on the background of varicose disease showed that the application of the drug combination of collagen and platelet-rich plasma significantly accelerates the epithelization of the wound surface, effectively stimulates granulation significantly reduces the negative sensations in the wound.

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