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NEW METHODS OF TREATMENT FOR TROPHIC LESIONS OF THE LOWER EXTREMITIES IN PATIENTS WITH DIABETES MELLITUS

Summary. Relevance. Complications in the form of trophic ulcers of the lower extremities are one of the serious consequences of diabetes mellitus (DM), as they often lead to severe health and social problems, up to high amputations. The aim of the study was the development and clinical testing of diagnostic and therapeutic algorithm for comprehensive treatment of trophic ulcers of the lower extremities in patients with DM. Materials and methods. Here are presented the results of treatment of 63 patients (42 women and 21 men) with neuropathic trophic lesions of the lower extremities or postoperative defects at the stage of granulation. Of them, 32 patients (treatment group) received local intradermal injections of hyaluronic acid and sodium succinate preparations (Lacerta) into the extracellular matrix. Patients of the comparison group were treated with hydrocolloid materials (hydrocoll, granuflex). In patients, the level of glycated hemoglobin, degree of circulatory disorders (by determining ankle brachial index, before and after the load test) and neuropathic disorders (on a scale for evaluation of neurologic dysfunction – NDS (Neuropathy Disability Score)) were assessed. Results of treatment were assessed by the rate of defect healing during 2 or more months. In the treatment group, 24 patients showed complete healing of the defect (75 %), while in the control group the healing was observed in 16 patients (51.6 %). Within a year, relapses occurred in 22.2 % of cases in the treatment group, and in 46.9 % – in the control one ($p < 0.05$). Conclusion. The developed method of treatment using Lacerta allowed to increase the efficacy of therapy, accelerate recovery and decrease a number of complications in patients with DM and trophic ulcers of the lower extremities.

Key words: diabetes mellitus, trophic ulcers of the lower extremities, method of treatment.

Introduction

As the prevalence of diabetes mellitus (DM) is increasing worldwide, the secondary complications associated with endocrine disorders are more common. Impaired glucose homeostasis and hyperglycemia lead to the activation of a number of pathological metabolic pathways, contributing to the development of vascular insufficiency and neurodegenerative processes in the lower extremities that cause a condition called diabetic foot syndrome (DFS) and requires special attention and careful treatment. This complication is one of the most pressing problems of modern diabetology [1-6], since it reduces the patient's quality of life and threatens serious consequences up to high amputations of the lower extremities.

Declared in 1989, consensus on the reducing the number of high amputations of the lower extremities by 50 % has not been achieved globally [6]. However, the experts from different countries try to develop a consensus to administer prevention and treatment of DFS and thereby reduce the number of amputations [5-9].

In May 2015 in Hague, an updated International Consensus on diabetic foot syndrome, which again emphasized the need for a multidisciplinary approach to the problem of lower limb lesions in DM, was achieved [6]. In particular, the principles of treatment of trophic ulcers were discussed as follows:

- 1) discharge of the affected foot;
- 2) restoration of blood flow;
- 3) treatment of inflammatory process;
- 4) metabolic control;
- 5) local treatment of ulcer;
- 6) informing patients and patients' relatives of the rules ulcer care;
- 7) prevention of recurrent ulcers.

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As for the local treatment of ulcers, it was noted that the drugs such as biologically active products (collagen, growth factors, and bioengineering tissues) are not used in routine practice. At the same time, numerous studies of this drug group are widely covered at both foreign and domestic congresses, in particular, of epidermal equivalent, Integra, Apligraft [3-5] and so on. Currently, pathogenetic local treatment of ulcers depending on the lesion's type and area and other factors has been postulated [3].

The aim of the above study was to improve the results of treating patients with neuropathic diabetic foot syndrome and postoperative defects, including by using hyaluronic acid preparation with sodium salt of succinic acid (Lacerta) [2].

Materials and methods

In the clinic of the Department of Disaster Medicine, Military Medicine, Anesthesiology and Resuscitation in Zaporizhzhia State Medical University and SI "Institute of Endocrinology and Metabolism named after V.P. Komisarenko of the NAMS of Ukraine", 63 patients with neuropathic DFS, whose average age was 46.4 ± 0.8 years, were treated from 2013 to 2015. The majority of patients suffered from type 2 DM (62 persons). 42 (66.7 %) were females and 21 (33.3 %) – males. Most patients (61 (95.2 %)) were represented by patients with neuropathic trophic lesions of the lower extremities or postoperative defects at the stage of granulation and met P-1, D-1 and D-2, I-1 and I-2, S-1 and S-2 according to PEDIS classification. With regard to the plane geometry (E), the ulcer area ranged from 0.75 to 5 cm². Abnormalities specific to diabetic peripheral polyneuropathy were assessed on the Neuropathy Disability Score (NDS) [1, 4]. Impaired blood flow in the lower extremities was evaluated by determining ankle-brachial index (ABI) before and after the load test [1, 4, 5]. Clinical efficacy of treatment was assessed in two months.

Table 1. Characteristics of study groups ($M \pm m$)

Parameters	Treatment group (n = 32)	Control group (n = 31)
Duration of DM (yr)	10.1 ± 1.2	9.8 ± 0.8
HbA1c, %	8.1 ± 0.9	7.9 ± 1.1
NDS (score)	12.4 ± 0.8	13.2 ± 0.9
ABI (a. dosalis pedis) before test	1.10 ± 0.03	1.00 ± 0.04
ABI (a. dosalis pedis) after test	1.20 ± 0.09	1.20 ± 0.05

All patients signed informed consent to participate in the study, agreed with the Bioethics Committee of SI "Institute of Endocrinology and Metabolism named after V.P. Komisarenko of the NAMS of Ukraine".

Statistical processing of the results was performed by means of the standard Excel analytical package (descriptive statistics) using Student's t test. The differences in parameters were considered significant at $p < 0.05$. Normality of distribution of the results obtained was verified using Shapiro-Wilk test.

Study results

Depending on the used method of treatment, the patients were divided into two groups, the characteristics of which are listed in the Table 1. There was no significant difference in initial clinical and laboratory parameters between two groups of patients.

Combination treatment of patients in two groups was consistent with general principles of therapy for trophic lesions, provided in International Consensus on DFS (2015) [6-8], namely:

- discharge of the affected extremity by means of Air cast (special shoes that a patient can take off at night and in order to change the dressing);
- antibiotic therapy (treatment regimen included antibiotics, to which the pathogens of inflammatory process were susceptible, following the biopsy of ulcer with further bacterial assay);
- local treatment of control group, consisted of the use hydrocolloid materials (hydrocoll, granuflex) and non-adhesive dressings (sterifix, suspurderm). In the study group, a hyaluronic acid preparation with sodium salt of succinic acid (Lacerta) was used 1-2 times a week.

The drug was administered after the onset of granulations or in the presence of chronic ulcers with the signs of good granulations. The ulcers were not accompanied by clinically proven osteomyelitis and severe inflammation process. Ulcers had predominantly pressor nature and were localized on the sole of the foot. Before administration of the drug, the ulcer was cleaned of hyperkeratosis, watered with saline and thoroughly dried with a sterile gauze pad. The drug was injected in the edges of the ulcer, holding a syringe at an angle of 45°. The next step was the application of aseptic dressings.

The results of treatment were assessed by the rate of defect healing within two months or more. Most patients with healed ulcers were monitored on ulcer relapse within a year of healing.

Within 2 months of treatment, the scores on NDS did not significantly change in patients of both groups. Moreover, no significant changes in ABI were observed. Lacerta tolerance was satisfactory (no allergic/adverse reactions in the treatment group were detected).



Figure 1. Changes in the size of trophic ulcer in monotherapy with Lacerta

For two months, complete defect healing was observed in 24 (75 %) of 32 patients of the study group and healing – in 16 patients (51.6 %) of the control group.

During a year, relapses occurred in 22.2 % of the treatment group and in 46.9 % of the control group ($p < 0.05$).

Example 1. Patient Sh., female, 1955, medical record No. 17145, was admitted to the Department of thermal injury and plastic surgery and diagnosed with the following: decompensated 2 type diabetes mellitus. DFS. Neuropathic form. Date of admission: 16.10.2012. Date of discharge: 16.11.2012. At admission, the patient complained of persistent trophic ulcer on the sole of the left foot, paresthesia, and burning pain in both legs. Medical history: ill since 1980, when D2M was diagnosed. Repeatedly took the courses of conservative treatment with vasoprotective drugs, metabolites, antiplatelet agents, preparations of α -lipoic acid; underwent amputation of the fourth and fifth fingers of both feet for osteomyelitis. Since 2008, she reported the deterioration when the aforementioned complaints occur. In a community hospital, she received a course of conservative treatment according to standard regimen – without the expected result. Complaints maintained. Patient was admitted to hospital for treatment.

Results of local examination: the skin and the temperature of both lower extremities are normal; peripheral sensitivity is reduced; peripheral pulse on both feet; deformed foot and ankle joints; trophic ulcerative defect 4×3 cm in diameter with callous edges and hyperkeratosis around in the center on the sole of the left foot. Debridement of defect, excision of hyperkeratosis, and applied dressing with antiseptic were performed.

On 17.10.12, the course of injections of hyaluronic acid with sodium salt of succinic acid was initiated. In the setting of dressing room, the patient's area of the ulcer was treated with antiseptic solution. Prior to treatment, the size of the defect was measured using the tape. Ready-to-use pre-filled glass Luer-lock syringe and extra needle with solution of unstructured hyaluronic acid with succinate (hyaluronic acid concentration: 15 mg/ml) were used. 0.5 cm away from the ulcer edges, an intracutaneous injection of 0.1-0.2 ml of the solution was performed once, using a tunneled method. The intervals between injection sites were 0.5 cm. A sterile gauze dressing was applied to the wound lesion. The procedure was repeated twice a week with mandatory ulcerative lesion measuring and photographing. The treatment course lasted 4 weeks.

Complete epithelialisation of trophic ulcer was reported after the treatment (Fig. 1). The patient was recommended wearing protective gauze dressing and full discharge of the foot – orthopedic shoes and crutches for two weeks.

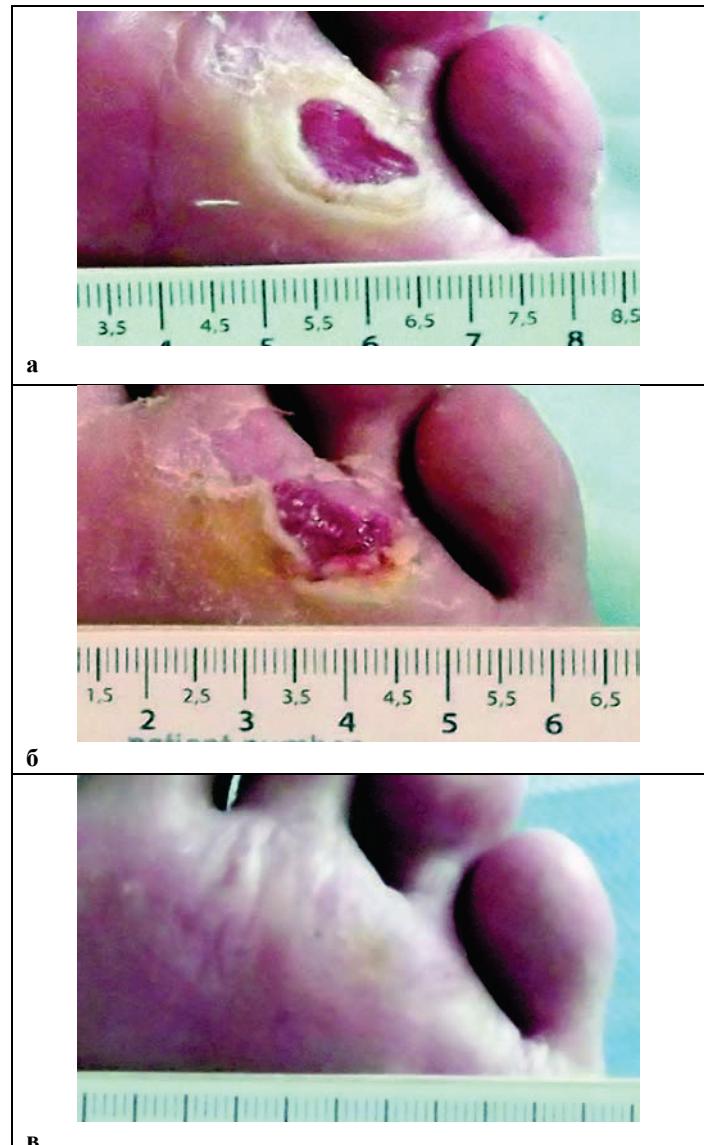


Figure 2. Results of treatment of patient N. showing complete epithelialization of trophic ulcer

Example 2. Patient N., female. Diagnosis: 2 type diabetes mellitus, diabetic foot syndrome. Trophic ulcer of the sole of the foot (P-1, E = 2 cm², D-2, I-1, S-2). Monotherapy with Lacerta was performed once a week. Complete healing was reported after 4 weeks (Fig. 2).

Discussion of results

Injection of hyaluronic acid preparations in extracellular matrix provides the site of surgery with additional amount of hyaluronic acid to optimize the performance of its biological functions in the skin, such as: increased turgor and tissue flexibility and stimulated processes of elastogenesis, collagenogenesis and angiogenesis. Sodium succinate (sodium salt of succinic acid) acts at the level of mitochondria and allows to activate the processes of cellular respiration and the synthesis of ATP and structural proteins of the skin.

This method of treatment can be used not only in hospitals but also in outpatient setting, which significantly reduces treatment time and patient's hospital stay.

Although this method demands special training, its further use does not require specific tools, anaesthetic support or operating room. Besides the fact that administration of this method does not require special tools and involvement of other professionals, it can be used in outpatient setting in order to treat existing trophic ulcers of vascular etiology in combination with surgical intervention. Due to the complex of positive effects, the method provides the opportunity to increase the efficacy of treatment, accelerate the recovery of patients and reduce the number of complications.

The data obtained warrants for further research of Lacerta as one of the components of a combination treatment of neuropathic and postoperative ulcerative lesions.

Conclusion

Proposed diagnostic and therapeutic algorithm involves determining the level and degree of circulatory and neuropathic disorders, optimization of surgical and local treatment of skin lesions, improves the results of combination treatment of diabetic foot syndrome, accelerating the healing of trophic ulcers, reducing the number of relapses during the year of observation compared with the group of patients receiving conventional treatment of this disease.

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