

Treatment Peculiarity of the Chronic Trophic Ulcers with Different Pathogenic Mechanism

Leczenie cech specyficznych przewlekłych owrzodzeń troficznych o różnym mechanizmie patogennym

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SUMMARY

Introduction: Trophic ulcers of the lower extremities are an unresolved problem of modern medicine. The treatment of this pathology requires new methods that optimize care regimens and improve patients' quality of life.

Aim: The study to improve efficacy of treatment of the patients with trophic ulcers of the lower limbs with consideration to pathogenesis.

Materials and Methods: The study included 32 patients with chronic venous disease C6 (1st group) and 31 with diabetes mellitus type 2, moderate severity, compensation stage with diabetic foot syndrome II stage according to Wagner's classification (2nd group). In addition to basic therapy in both groups photodynamic therapy was added at the first stage of the study, and at the second stage plasma rich in growth factors was prescribed.

Results: At baseline evaluating of the chronic venous disease demonstrates that a total score in patient of the 1st group was 20,9 points on a modified VCSS scale; after two weeks – 15,71 points (improvement by 24.83%), and 6 weeks after – 9,72 points (improvement by 53.49%). In patients with DM (2nd group) at the baseline a total score average was 13,91 points according to S(AD)SAD-1 scale; after 2 weeks – 12,29 (improvement by 11,65%), after 6 weeks – 6,39 points (improvement by 54,06%).

Conclusions: The inclusion of photodynamic therapy and plasmatherapy in complex therapy in both groups led to a significant improvement of the healing process and helps to reduce the depth and area of the wound surface. However, the wound healing in patients in group 2 was slower.

Key words: diabetes mellitus, chronic venous disease, trophic ulcers, photodynamic therapy, autologous plasma

STRESZCZENIE

Wstęp: Wrzody troficzne kończyn dolnych stanowią nierozwiązany problem współczesnej medycyny. Leczenie tej patologii wymaga nowych metod, które zoptymalizują schematy opieki i poprawią jakość życia pacjentów.

Materiał i metody: W badaniu wzięło udział 32 pacjentów z przewlekłą chorobą żylną C6 (1 grupa) i 31 z cukrzycą typu 2, o umiarkowanym nasileniu, z zespołem stopy cukrzycowej na II etapie wyrównania według klasyfikacji Wagnera (2 grupa). Oprócz podstawowej terapii w obu grupach na pierwszym etapie badania dodano terapię fotodynamiczną, a na drugim etapie zalecono podanie osocza bogatego w czynniki wzrostu.

Wyniki: W początkowej ocenie stopnia nasilenia choroby żył wykazano, że całkowity wynik u pacjenta z pierwszej grupy wynosił 20,9 punktów w zmodyfikowanej skali VCSS; po dwóch tygodniach – 15,71 punktów (poprawa o 24,83%) i po 6 tygodniach po – 9,72 punktów (poprawa o 53,49%). U pacjentów z DM (2 grupa) na początku badania całkowity wynik wynosił 13,91 punktów zgodnie ze skalą S (AD) SAD-1; po 2 tygodniach – 12,29 (poprawa o 11,65%), po 6 tygodniach – 6,39 punktów (poprawa o 54,06%).

Wnioski: Włączenie terapii fotodynamicznej i plazmaterapii do kompleksowej terapii w obu grupach doprowadziło do znacznej poprawy procesu gojenia i pomogło zmniejszyć głębokość i obszar powierzchni rany. Jednak gojenie się ran u pacjentów w grupie 2 było wolniejsze.

Słowa kluczowe: cukrzyca, przewlekła choroba żylna, owrzodzenia troficzne, terapia fotodynamiczna, osocze autologiczne

INTRODUCTION

According to World Health Organization, diabetes mellitus (DM) affects about 422 million people worldwide [1]. About 20% of people with DM develop trophic ulcers (TU) that lead to amputation in 4-10% [2]. In patients with chronic venous disease (CVD), TU are found in 2% of adults, and in patients older than 65 years of age, this figure rises to 3-6% [3].

Treatment options of trophic disorders of any etiology includes local treatment of the wound defect, pathogenic therapy, and surgery. Autodermoplasty and surgical treatment are widespread in the management of TU. Despite the efficiency of these methods, in some clinical situations they cannot be used, and in 25-40% of cases they lead to complications such as skin necrosis, rejection and lysis of autodermal flaps [4]. In 11% of patients, surgical treatment is associated with 2-4 cases of relapse within 1 year. A particular problem is the treatment of patients of advanced age; such treatment is long term and has insensitive to the therapy. That is why recently there is an increasing interest in developing and advancing the methods of TU treatment with the aim to improve the healing process and prevent relapses.

AIM

The aim of the study to improve efficacy of treatment of the patients with trophic ulcers of the lower limbs with consideration to pathogenesis.

MATERIAL AND METHODS

The study involved 63 patients, 32 with chronic venous disease C6 EpAsPr (1st group) and 31 with diabetes mellitus type 2, moderate severity, compensation stage with diabetic foot syndrome II stage according to Wagner's classification (2nd group).

Basic therapy in both groups included wound defect debridement, antibiotic therapy (according to the results of wound discharge microbiological examination), vasoactive agent, compression stockings of different compression grades, topical treatment (ointment compositions considering the phase of trophic ulcer healing). In the 2nd group compensation of glycemia was achieved through the use of oral hypoglycemic agents and insulin [5, 6].

Considering the chronic character of trophic ulcers, patients of both groups was prescribed with photodynamic therapy (PDT) at the first stage of the study. PDT was performed with laser machine "Lika-Surgeon M" (Photonica - Plus, Cherkasy, Ukraine) with wavelength of 660 nm in a continuous regiment. The power of 0,8-1,5 W and fluence of 20-30 J/cm² was used. Energy density for 1 procedure was 300 - 450 J depending on the size of the wound defect area. Methylene blue 1% aqueous solution was used as a photosensitizer. This treatment course included 8 procedures, which were performed every other day.

Plasmatherapy was added to the next stage of the complex treatment to stimulate epithelialization. 18 ml of blood from the patient's cubital vein was centrifuged at 3000 rev/minute, and 12 ml of autologous plasma rich in growth factors was obtained. Luer lock 3.0 ml syringe with interchangeable needle of 30 G 0.3x4 mm was used for intradermal injection up to 4

mm depth (into the reticular layer of the dermis) with 5 mm interval by the peripheral margins of the wound according to epithelialization zone edges. Needle of 30 G 0.3x13 mm was used to the profound (4-6 mm) administration of plasma in direction from the periphery to the center. The intradermal injections course included 4 procedures once a week.

To evaluate results, clinical severity score VCSS was used in the 1st group; and the S(AD)SAD classification was used in the 2nd group at the baseline (VCSS-1; SAD-1), after two weeks (VCSS-2; SAD-2), and 6 weeks after the treatment (VCSS-3; SAD-3).

VCSS score evaluates the following attributes: pain, varicose veins, venous edema, skin pigmentation, inflammation, induration, number, size, and duration of active ulcers, and compressive therapy on a scale of 0-3. These items were scored in terms of severity on a 3-point rating scale ranging from 0 (absent) to 3 (severe) with a maximum score of 30 [7].

S(AD)SAD classification (Size (Area, Depth), Sepsis, Arteriopathy, Denervation) includes 4 categories, 2 points for each, with a maximum score of 30 points that characterize the most severe condition [8]. Size (0 - skin intact; 2- <1 cm²; 4 - 1-3 cm²; 6 - >3 cm²) and depth of the wound surface (0 - skin intact; 2- superficial - involving skin and subcutaneous tissues but not reaching to tendon, periosteum or joint capsule; 4 - penetrating to tendon, periosteum or joint capsule; 6 - involving bone or joint spaces), infection process (0 - no infection; 2- surface infection, indicated by slough or exudate, but without clinical suspicion of cellulitis or osteomyelitis, also tinea pedis; 4 - cellulitis; 6 - osteomyelitis), and angiopathy were evaluated by using ankle-brachial index (ABI) where 1 point was for 0.7-0.9, and 2 points - for ≤ 0.6; neuropathy was evaluated by using neurological deficit score (NDS): a score of 0 indicated no neuropathy, a score of 1 moderate neuropathy, and a score of 2 severe neuropathy.

The ulcer surface area was evaluated by using LesionMeter app for electronic devices that precisely measures the wound surface area and creates data base. Measurements were performed at the baseline and at each next visit of the patient to allow estimate the progression of epithelialization. A standard bank card placed near the ulcer was used for scaling during photographic record. Digital information and graphics images obtained were saved automatically in separate folders.

Statistical analysis was performed with Windows 10 - Office Professional Plus software (Agreement ID: V0731528) with the use of parametric and non-parametric methods of variation statistics. Shapiro-Wilk test was applied to test normality of parameters in the study. Two-sample Student's t-test was used to determine the significantly changed between groups with a probability mean of 0.05. Relative changes method was used to compare ulcers healing dynamics in two groups.

RESULTS

Baseline evaluating of the vein disease severity demonstrate that a total score severity VCSS in patient of the 1st group was 20,9 points on a modified VCSS scale; after two weeks - 15,71 points (improvement by 24.83%), and 6 weeks after - 9,72 points (improvement by 53.49%) (Table1).

Table 1. VCSS evaluation of ulcers healing dynamics in the 1st group

Group	Pain	Varicose veins	Venous edema	Skin pigmentation	Inflam-mation	Induration	Number of active ulcers	Size of active ulcers	Duration of active ulcers	Compressive therapy
At baseline	2.94	2.06	2.09	1.97	2.88	2.06	1.06	1.97	2.78	1.09
2 weeks	0.94	2.06	0.81	1.97	1.00	1.09	1.06	1.97	2.78	2.03
6 weeks	0.06	2.06	0.03	1.97	0.03	0.03	0.13	0.13	2.78	2.50

Table 2. Relative percentage changes in the 1st group according to VCSS dynamic

Group	Pain	Varicose veins	Venous edema	Skin pigmentation	Inflam-mation	Induration	Number of active ulcers	Size of active ulcers	Duration of active ulcers	Compressive therapy
2 weeks	-68.09	0.00	-61.19	0.00	-65.22	-46.97	0.00	0.00	0.00	85.71
6 weeks	-97.87	0.00	-98.51	0.00	-98.91	-98.44	-88.24	-93.65	0.00	128.57

The clinical status in patients with CVD (1st group) was improved due to reduction of pain syndrome from 2,94 to 0,94 point (2 weeks), from 0,94 to 0,06 point (6 weeks); venous edema - from 2,09 points (lower leg or thigh) to 0,81 point (foot or no venous edema) in 2 weeks, from 0,81 to 0,03 point in 6 weeks; induration from 2,06 to 1,09 point (2 weeks), from 1,09 to 00,03 point (6 weeks); inflammation - from 2,88 to 1 points (2 weeks), from 1 to 0,03 point (6 weeks). Totally, effectivity of combine

treatment with PDT and plasmatherapy in the 1st group was confirmed with method of relative percentage changes (Table 2).

No statistically significant reduction of the ulcer surface area at the first stage was observed in patients of the 1st group ($p \geq 0.05$). Surface area reduction 6 weeks after the treatment has revealed 0 point (no active ulcers) in 28 patients, while in the remaining 4 patients, the size of active ulcers was of 1 point (Figure 1, 2).



Figure 1. Ulcer in a Patient with Chronic Venous Disease C6 EpAsPr, view at baseline

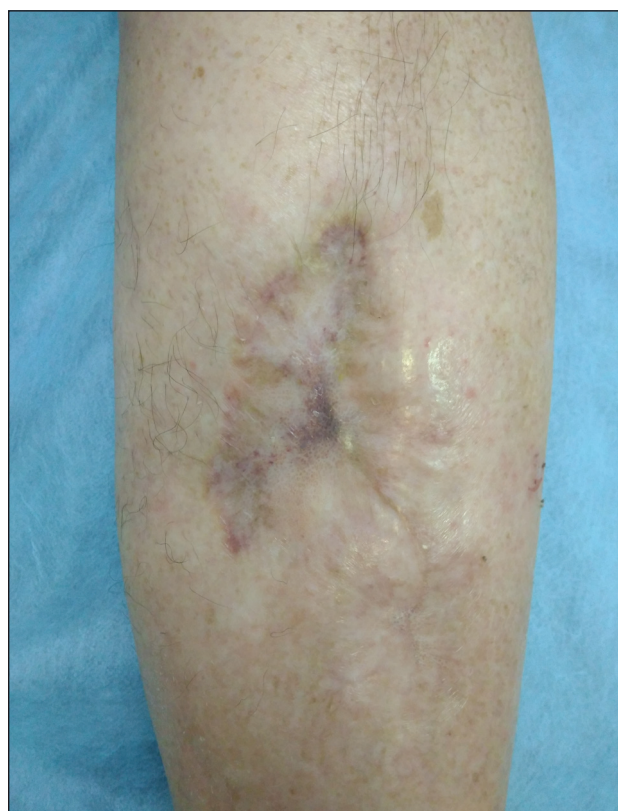


Figure 2. Ulcer in a Patient with Chronic Venous Disease, view in 6 weeks after combined treatment

Table 3. S(AD)SAD evaluation of ulcers healing dynamics in the 2nd group

Group	Size of the wound surface	Depth of the wound surface	Infection proces	Angiopathy	Neuropathy
At baseline	4.26	2.00	3.81	1.94	1.90
2 weeks	4.26	2.00	2.19	1.94	1.90
6 weeks	2.00	1.81	0.00	1.10	1.48

Table 4. Relative percentage changes in the 2nd group according to S(AD) SAD

Group	Size of the wound surface	Depth of the wound surface	Infection proces	Angiopathy	Neuropathy
2 weeks	0.00	0.00	-42.37	0.00	0.00
6 weeks	-53.03	-9.68	-100.00	-43.33	-22.03

In patients with DM (2nd group), clinical severity on S(AD) SAD-1 scale was evaluated at the baseline, a total score average score was 13,91 points; after 2 weeks – 12,29 (improvement by 11,65%), after 6 weeks – 6,39 points (improvement by 54,06%) (Table 3).

Improvement of clinical status in patients of the 2nd group was achieved through the reduction of the infection process from 3,81 to 2,19 points (2 weeks); from 2,19 to 0 point (6 weeks).

On first stage, there was no significant change in the figures of area (average score 4,26 points) and depth of the ulcer defect (average score 2 points) and also in manifestation of angio- and neuropathy ($p \geq 0.05$).

Sensorimotor disorders evaluated on NDS scale showed moderate neuropathy at 1,9 points (index on NDS scale was 5-13 points) vs 1,48 point after 6 weeks (Table 4). simultaneously angiopathy has reduced from 1,94 to 1,1 point (ABI as $\geq 0.7-0.9$).

Use of the plasmatherapy at the second treatment stage (2-6 weeks) has improved the healing of the wound area from 4,26 to 2 points and depth from 2 to 1,81 points (Figure 3, 4), which has been demonstrated by method of relative percentage changes (Table 4).

DISCUSSION

Social significance of chronic trophic ulcers of any etiology lies in decrease physical and professional activities, reduced quality of life, and in patients with diabetic foot syndrome – in the increased number of amputations, disability, and death rate. Comorbid nature of trophic ulcers of the lower limbs caused by various pathogenic mechanisms leads to chronicity of the process and long-term recurring.

There is not enough information to compare the mechanisms and indicators of the healing of trophic ulcers in diabetes mellitus and chronic venous diseases; and there is no exact statistics on the combination of two diseases.

According to different authors [9-12] an average trophic ulcer healing time with adequate therapy is about 20-48 weeks. Long-term administration of antibiotics is sometimes

**Figure 3.** Ulcer in a Patient with Type 2 Diabetes Mellitus, view at baseline**Figure 4.** Ulcer in a Patient with Type 2 Diabetes Mellitus, view in 6 weeks after combined treatment

ineffective; especially in diabetes mellitus patients. 25-50% of ulcers of the lower limbs do not heal completely for 6 months, and the rate of non-traumatic amputation reaches 10-15% [13-16].

The study found that the process of re-epithelialization of the wound surface and the transition to the granulation

phase in patients of 1st group was 62.5% faster compared to 2nd group, and epithelialization was 45% faster in 1st group compared to the patients of 2nd group.

CONCLUSIONS

The duration of trophic ulcers healing process is related to not only the localization of the ulcer defect, its depth, area, and persistence, but also to pathogenic mechanism that has caused trophic ulcers. A combined treatment regimen with PDT at the first stage of ulcer healing and plasmatherapy at the second stage may be considered as the supplementary approach to traditional regimens to improve treatment algorithm.

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Conflicts of interest:

The Authors declare no conflict of interest

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