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Efficiency and Safety of Collagen Biomaterial in Treatment of Diabetic Foot Syndrome

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Abstract

Object:
To improve the results of treatment of patients with diabetic foot syndrome, including the use of collagen biomaterial.

Materials and methods.
We have made a multicentre study with the participation of 71 patients with diabetic foot syndrome of different severity levels. The patients were randomized into two homogeneous groups: 1) group of standard therapy (n=35); and 2) group with additional administration of collagen biomaterial (Collost/Salvecoll) (n=36). The dynamic assessment of patients was performed when including into the study and on the 7th, 14th and 28th day of treatment.

Results.
The use of collagen biomaterial was attended by the faster and more effective healing of the ulcerative defect. The wound area decreased mainly due to reduction in its width, while the success of the treatment increased 1.7 times. The additional use of collagen biomaterial led to a significant increase in the incidence rate of complete epithelialization of the defect against the background of a reduction in the incidence rate of ineffective treatment. The correlation analysis performed has shown that a favorable result expressed in a good or complete wound/ulcer healing is associated with small defect size, Wagner II without signs of pronounced infection and ischemization and with the use of collagen biomaterial.

Keywords: diabetic foot syndrome, trophic ulcer size, epithelialization, collagen, Collost, Salvecoll.

INTRODUCTION

Nowadays the incidence of diabetes mellitus (DM) shows a fast growth, becoming a global epidemic. The number of people suffering from DM has exceeded 350 million, while according to the forecasts in the next 25 years the number of DM patients will reach 550 million [1]. The high incidence of the disease, the long-term morbidity and frequent development of complications determine the burden of DM. One of such complications contributing to disability and social disadaptation is diabetic foot syndrome (DFS) [2]. The global prevalence of DFS is 6.3% [3].

The development of DFS is based on vascular pathology and diabetic neuropathy [4-5], as a result of which a lack of pain syndrome and a late diagnosis of the disease become usual "companions" of DFS. A major role in the pathogenesis of the DFS belongs to the formation of a diabetic ulcer and to the introduction of bacteria into the place of the skin cover defect [6]. It is also possible to infect wounds of traumatic genesis or surgical wounds. The development of purulent inflammation and necrosis of affected tissues often cause amputation of the lower limbs. Therewith the five-year survival after amputation varies from 30 to 70% [7]. Even if the patient survives after the amputation of the lower limb, often such surgeries lead to disability of the patient which is connected with significant economic losses.

To achieve a clinical effect, the DFS treatment should be multidisciplinary and should be based on a multifactor approach [8-9]. The obligatory components of therapy are the normalization of carbohydrate metabolism, the improvement of blood supply to the affected limb, the elimination of loading onto the limb, antibiotic therapy and topical treatment [10-11]. In the topical treatment of diabetic ulcers, it is possible to detach the following stages: the sanitation stage and the stage of granulation and epithelialization stimulation. The surgical excisions of affected necrotic tissues with a scalpel, as well as the use of other various mechanical, chemical, physical and biological methods of sanitation, are also possible. However, despite the use of various therapies, the average duration of ulcers healing under the DM condition is quite long-term: in the case of ulcers localization in fingers and in the forefoot, the healing duration is about 150 days, while during the ulcers localization in the middle part of the foot the period of

healing increases to about 190 days; in the calcaneal region – to about 235-240 days [12-13], which indicates the need to clarify the existing treatment protocols and to develop new effective materials used for topical DFS therapy.

The **object** of this research is to study the effectiveness of the collagen biomaterial use during the treatment of patients with diabetic foot syndrome.

MATERIALS AND METHODS

In 2016, 71 patients with DFS aged 30-80 years old (average age 58.96 ± 8.11 years old; median – 60 years old) were included into a multicentre prospective comparative observational study, including 34 (47.9%) women and 37 (52.1%) men who underwent medical examination and treatment at hospitals and outpatient clinics in Moscow, St. Petersburg, Kazan, Vidnoye, & Lytkarino. The damage level among 50 patients (70.4%) corresponded to Wagner II and among 21 (29.6%) patients – to Wagner III. The duration of the ulcerative defect varied from 6 weeks to 2 years, 8.4 ± 9.1 months on the average (median – 6 months).

The following patients were not included (or were excluded) into the study: patients with DFS of Wagner I, IV, V; with DFS less than 6 weeks; with a found persistence of Ps. Aeruginosa/anaerobic infection in the wound; with critical lower limb ischemia; with hyperglycemia above 14 mmol/L; patients with chronic somatic diseases tolerant to the ongoing therapy at the stage of decompensation. Infectious diseases and burdened allergic anamnesis were also the criteria for exclusion.

The patients included into the study were randomized into 2 groups. The comparison group included 35 people (19 men and 16 women) who received standard treatment without the use of collagen biomaterial (surgical debridement, hydrocolloid dressings, unloading of foot, conservative pharmacotherapy). The main group consisted of 36 patients (18 men and 18 women) whose standard treatment was supplemented by the use of Collost/Salvecoll collagen biomaterial (gel, membrane). These groups of patients were homogeneous ($p > 0.05$) (Table 1).

The initial defect sizes of skin and soft tissues in both groups were comparable ($p > 0.05$). On the average (median) the length in the main group was 4.9 cm, while in the comparison group – 5.0 cm; the width was 2.8 and 3.0 cm, respectively; and the depth was 0.3 cm in both groups. The DFS area averaged 13.5 cm^2 in the main group (interquartile interval – 5.3/38.0 cm^2) and 12.6 cm^2 in the comparison group (interquartile interval – 7.5/35.0 cm^2) ($p > 0.05$); the DFS size was 4.6 cm^3 (interquartile interval – 1.8/15.3 cm^3) and 3.6 cm^3 (interquartile interval – 1.8/10.3 cm^3), respectively ($p > 0.05$).

The assessment of condition was performed in dynamics (visit 1 on the 1st day, visit 2 on the 7th day, visit 3 on the 14th day, visit 4 on the 28th day) and included the following methods: anamnesis and patient complaints; anthropometric measurements; blood pressure and heart rate; assessment of wound condition, including the measurement of its length, width, depth and wound area, Wagner classification, degree of a stage, photo-documentation; assessment of pain basing on a visual analog scale; determination of blood glucose level. When including into the study, all patients also underwent a radiograph of the foot in two projections; microbiological (bacteriological) examination of the wound; assessment of the state of macro- and microhemodynamics (ultrasound dopplerography (USDG) of lower limb arteries, oximetry); and a laboratory examination, including the determination of the level of glycated hemoglobin alongside with screening indicators of clinical and biochemical blood analysis.

Statistical processing of the study results was carried out using the SPSS 20.0 program with the implementation of standard parametric and nonparametric criteria for estimating the statistical significance. The differences were considered to be significant at $p < 0.05$. The descriptive statistics of qualitative parameters is presented in the form of frequencies (abs, %), quantitative – in median (Me), average ± standard deviation, and lower and upper quartile – in cases when the parameter had a distribution function far from the normal one. The normal distribution was considered to be the distribution with the Kolmogorov-Smirnov discrepancy criterion higher than 0.05. To compare two independent nonparametric samples we used the Mann-Whitney test, and for the multiple comparisons – the Kraskell-Wallis test. To compare two dependent non-parametric samples we used the Wilcoxon test and for the multiple comparisons – the Friedman test. Qualitative variables were compared using the $\chi 2$ test (Pearson chi-squared test, analysis of contingency table). The correlation analysis was performed under the Pearson method.

Table 1. The distribution of patients by age, sex, Wagner, duration of ulcer disease in both groups.

		Collost/Salvecoll	Comparison	Overall
Age (p=0.102)	M±m Me 25%/75% q	57.50±10.25 59 52/63	60.45±4.75 60 58/65	58.96±8.11 60 55/64
Sex (p=0.814)	- Male; n (%) - Female; n (%)	18 (50%) 18 (50%)	19 (54.3%) 16 (45.7%)	37 (52.1%) 34 (47.9%)
Wagner (p=0.443)	II; n (%) III; n (%)	27 (75%) 9 (25%)	23 (65.7%) 12 (34.3%)	50 (70.4%) 21 (29.6%)
Duration of DFS, months (p=0.263)	M±m Me 25%/75% q	9.54±9.74 6 3/12	7.39±8.47 5 2.5/10	8.40±9.09 6 3/12

RESEARCH RESULTS AND THEIR DISCUSSION

The results of the study have shown that the process of wound closure took place mainly due to the growth of the epithelium from its edges, i.e. directly in those areas where due to injections the maximum concentration of bioplastic material was continuously created, and thus the cells constantly received a biological signal as to the possibility and necessity of dividing. Thus, the wound length in the group of patients using collagen biomaterial within 4 weeks of observation decreased on average from 4.8 to 2.3 cm (regression averaged 2.09 times; $p < 0.05$). The reduction of wound length in the comparison group was lower (on average – from 5.0 to 3.9 cm, regression averaged 1.28 times; $p < 0.05$). The reduction of the wound width in the group of patients using collagen biomaterial was more pronounced (on average – from 2.8 to 1.0 cm within 4 weeks of observation, regression averaged 2.80 times; $p < 0.05$). The reduction of the wound width in the comparison group was the smallest one (on average – from 3.0 to 2.0 cm, regression – 1.5 times). In such a manner, by the end of the study a statistically significant difference between the groups has been two-times established ($p < 0.05$). The dynamics of changes in the wound depth was comparable in both groups.

The obtained effect has an undoubted interest for medical specialists, as it turned out that the form of the defect can itself cause reasonable optimism regarding the forecasted outcome or, vice versa, raise the contemplations on whether it is necessary to start thinking about the surgical methods of the current ulcerative defect correction in advance.

The result of significant improvement in healing of the DFS wound width in the Collost/Salvecoll group was the most pronounced dynamics of the wound area regression which has advanced the group of comparison (Figure 1). Thus, in the Collost/Salvecoll group the wound area has regressed on average (median) from 13.5 cm^2 at the 1st visit to 10.6 cm^2 at the 2nd visit (1.27 times), to 6.3 cm^2 at the 3rd visit (2.14 times) and up to 2.1 cm^2 at the 4th visit (6.43 times). In the comparison group the wound area has regressed from 12.6 cm^2 at the 1st visit to 12.5 cm^2 at the 2nd visit (1.01 times), to 10.0 cm^2 at the 3rd visit (1.26 times) and up to 7.0 cm^2 at the 4th visit (1.80 times). A statistically significant intergroup difference has been noted at the 4th visit, where the wound area in the comparison group was on average 3.33 times larger than the one in the Collost/Salvecoll group ($p < 0.05$).

The rate of the DFS wound/ulcer volume regression among the DFS patients using Collost/Salvecoll has also been the highest one and has significantly advanced the comparison group. Thus, in Collost/Salvecoll the volume of regression has averaged (median) from 4.64 cm^3 at the 1st visit to 2.94 cm^3 at the 2nd visit (1.58 times), to 1.30 cm^3 at the 3rd visit (3.57 times) and up to 0.34 cm^3 at the 4th visit (13.65 times). In the comparison group the volume of regression has averaged from 3.61 cm^3 at the 1st visit to 3.30 cm^3 at the 2nd visit (1.09 times), to 2.34 cm^3 at the 3rd visit (1.54 times) and up to 1.10 cm^3 at the 4th visit (3.28 times).

During the study, it was found out that the percentage of wound (ulcer) area reduction starting from the stage of including into the study and finishing with the 28th day of the treatment was on average 39% in the comparison group under the interquartile interval of 23/63%, and 67% in the main group under the interquartile interval of 49/93% (Figure 2).

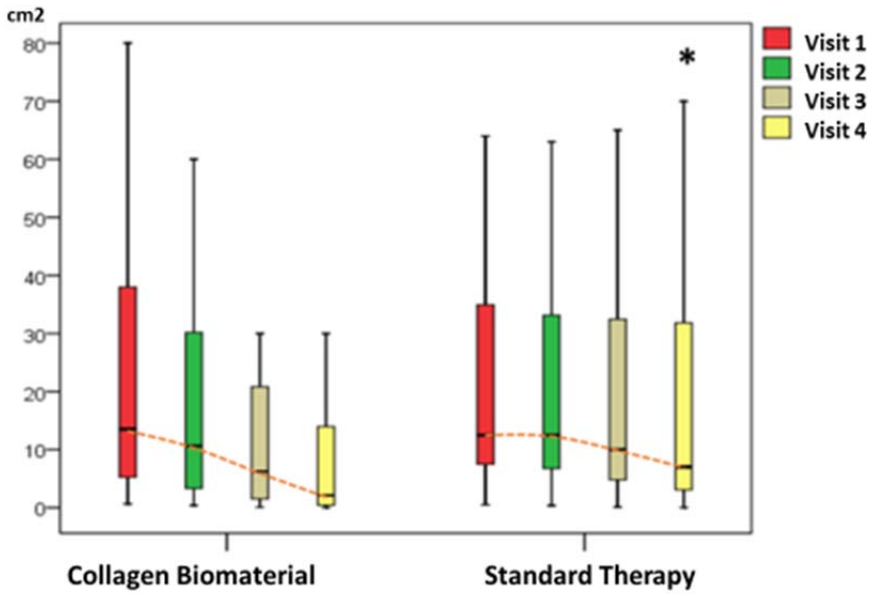

Figure 1. The dynamics of DFS wound area on the 1st, 7th, 14th and 28th day of the study in both groups
(– difference between groups when $p < 0.05$).*

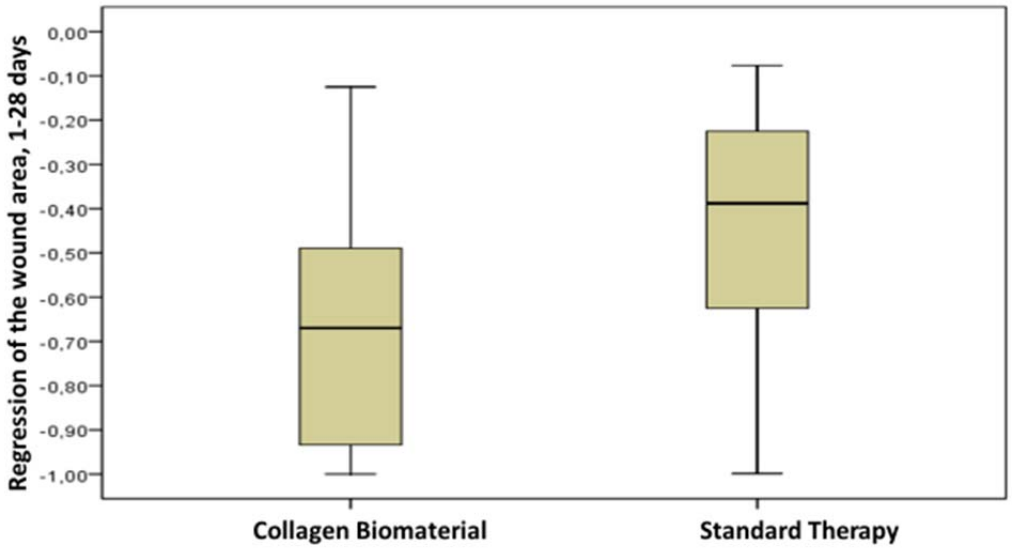

Figure 2. Reduction of wound area (ulcers) starting from the stage of including into the study and finishing with the 28th day of treatment in both groups (n=71; $p < 0.05$)

Table 2. The incidence rate of complete epithelialization and ineffective treatment in both groups by the 28th day ($p < 0.05$; x2)

		Collost/Salvecoll	Comparison	Overall
Complete epithelialization	ABS	8	3	11
	% result	72.7%	27.3%	100.0%
	% group	22.2%	8.6%	15.5%
Average result	ABS	25	20	45
	% result	55.6%	44.4%	100.0%
	% group	69.4%	57.1%	63.4%
Ineffective treatment	ABS	3	12	15
	% result	20.0%	80.0%	100.0%
	% group	8.3%	34.3%	21.1%

By the 28th day of the study, the complete epithelialization has been noted in 11 cases (15.5%), including 8 cases in the Collost/Salvecoll group (22.2%) and 3 cases among the patients from the comparison group (8.6%). The absence of epithelialization or healing of the wound area by less than 25% from the initial indicator by the 28th day has been noted in 15 cases (21.1%), including 3 cases in the Collost/Salvecoll group (8.3%) and 12 cases among patients from the comparison group (34.3%). Consequently, the administration of the Collost/Salvecoll biomaterial within the DFS standard therapy has in a month of treatment resulted in the increase of incidence of wound complete epithelialization by 2.58 times upon the simultaneous reducing of incidence of ineffective treatment by 4.13 times (Table 2).

The performed correlation analysis has confirmed a number of established truths. The outcome depends on the depth of the damage, the sizes of the wound/ulcer (its length and width, area and volume at all visits), stage, extent and depth of injury, and the availability of hemodynamically significant stenosis in the lower limbs arteries.

A favorable outcome is connected with a background small ulcer defect sizes, with a Wagner II damage level, lack of significant infection and wound/ulcer ischemia factors. The success attended the patients without hemodynamic disorders determined by instrumental studies, and the patients who received additional Collost/Salvecoll treatment. The last one once again underscores the effectiveness of collagen-containing drugs usage in the treatment of patients with DFS who use a biological marker habitual for cells.

The adverse outcome (non-healing or weak healing of ulcerative defect <25%) is reliably related to large background sizes of DFS, to the depth of damage, Wagner III and hemodynamically significant blood supply disturbance of the limb. At the same time, the outcome has worsened proportionally to the stage and extent of the damage, as well as to the level of limb amputation that was made regarding the previously conducted unsuccessful DFS treatment. In addition, an adverse outcome by the 28th day of treatment has been noted among the patients who at the 1st visit had a low level of red blood cells, segmented neutrophils and protein, and among the patients with high lymphocyte count. This indicates the significant role of the immune system and protein metabolism in the pathogenesis of diabetes mellitus and DFS.

Despite the established opinion on the importance of assessing the level of glycosylated hemoglobin (as well as the blood glucose level) to forecast the wound healing, the analysis carried out during a short time period of patient observation didn't confirm this idea.

CONCLUSION

Thus, the use of Collost/Salvecoll biomaterial is an effective and safe way to treat DFS. The adding of Collost/Salvecoll biomaterial to the standard methods of treatment of patients with DFS safely accelerates the healing of the wound surfaces and increases the number of favorable results.

At the same time, there are a number of questions that were not raised while planning the study, but arose in the process of its conducting. Thus, as a result of performing the multifactor correlation analysis it was found out that, in addition to the ulcer size, the important predictive signs of the forthcoming treatment success are: the severity of organ ischemia caused by the damage of the lower limbs vessels and/or non-stemorrhagic anemia; the lack of an adequate immune response characterized by a decrease in the number of mature phagocytes (segmented neutrophils); and the absence of young leukocyte forms. The lymphocytosis noted among these patients makes us think over the attempts of the body to apply the immune defense mechanisms; however, these processes apparently do not end with the synthesis of cytokines. Taking into account that hypoproteinemia and dysproteinemia have also been noted among the same patients, it becomes obvious that the cause of all disorders of immunity is in the development of various protein synthesis disorders.

The carried out correlation analysis of the data obtained during the study has revealed several objective laboratory factors that have never been previously taken into account when treating the patients with DFS, and are not reflected in the standards of medical care delivery. A close correlation relationship proved during the analysis of the material in the presented group of the patients is a strong confirmation of the need to continue the research in this direction in order to take another one step towards the personalized medicine.

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