

LOCAL CYTOKINE THERAPY FOR DIABETIC FOOT SYNDROME

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ABSTRACT

Background. In recent years, the use of cytokines and various growth factors in the treatment of chronic wounds in patients with diabetes mellitus has been of great interest. This manuscript is devoted to this particular problem, which made it possible to improve the results of treatment. **Material and methods.** The results of the treatment of 72 patients with type 2 diabetes mellitus with diabetic foot syndrome are presented, consisting of two groups: the main group (38 patients who, along with the standard treatment of diabetic foot syndrome, underwent local applications with a solution of the immunomodulator Superlymph according to the generally accepted scheme) and the comparison group (34 patients who used traditional treatment for this pathology). Clinical, laboratory and instrumental research methods available in clinical settings were used. **Results and conclusions.** A change in the local cytokine status in the form of a decrease in anti-inflammatory and an increase in pro-inflammatory cytokines is characteristic of patients with diabetic foot syndrome. The levels of cytokines of wound discharge exudate depend on the duration of diabetes mellitus, and the level of glycated haemoglobin and leukocytosis and do not depend on the form of diabetic foot syndrome. The use of Superlymph in the complex therapy of patients with diabetic foot syndrome contributes to the normalization of the immune status, which in turn ensures effective healing of ulcerative foot defects in diabetic foot syndrome.

Key words: Type 2 diabetes mellitus, diabetic foot syndrome, cytokines, cytokine therapy.

INTRODUCTION

According to the World Health Organization, there are currently about 180 million patients with diabetes in the world. Calculations have shown that, in the case of an increase in the average life expectancy to 80 years, the number of patients with diabetes mellitus can reach 17% of the total population [1, 3, 4, 22, 24, 31].

Given the chronic incurable course of the disease and the increasing average life expectancy of patients, research aimed at developing methods for diagnosing,

preventing and treating late complications of diabetes mellitus is becoming increasingly important [19-21, 23, 25, 30, 37, 38]. One of the complications of diabetes mellitus, which most often leads to disability and a decrease in the quality of life of patients, is diabetic foot syndrome [7-9, 10, 11, 14, 18, 32, 33, 36].

If earlier it was traditionally considered the trigger mechanism and the main factor in these processes of carbohydrate metabolism disorders, then from modern positions, immune mechanisms began to play a significant role in the pathogenesis of diabetic foot syndrome - a decrease in the number and activity of T-lymphocytes, a violation of the phagocytic link, as well as an imbalance of cytokines: an increase in pro-inflammatory and a decrease in anti-inflammatory cytokines [15, 27, 29].

All of the above substantiates the relevance of the problem and the feasibility of the study to study the possibility of using cytokines and growth factors in patients with diabetic foot syndrome.

MATERIALS AND RESEARCH METHODS

The present study included 72 patients with type 2 diabetes mellitus with diabetic foot syndrome, who made up two groups: the main group and the comparison group. The main group included 38 patients who, along with the standard treatment of diabetic foot syndrome, underwent local applications with a solution of the immunomodulator Superlymph according to the generally accepted scheme. The comparison group consisted of 34 patients who used traditional treatment for this pathology.

Of the 72 patients included in the study, 43 (63.5%) were women and 29 (36.5%) were men. The age of the patients ranged from 52 to 78 years, the average age of the patients of the main group was 66 ± 7.9 years, and the comparison group was 65.4 ± 6.6 years. The duration of type 2 diabetes mellitus in patients of the main group averaged 11.5 ± 6.2 years, and the comparison group - 12 ± 6.3 years. All patients underwent drug therapy for diabetes mellitus before hospitalization: 31 patients (43%) received insulin therapy, 17 patients (23.6%) received oral hypoglycemic drugs, and 24 patients (33.4%) received combination therapy. The mean level of glycated haemoglobin (HbA1c) in the study group was $10.5\pm 1.4\%$, and in the comparison group - $10.5\pm 1.2\%$.

Taking into account the specifics of the hospital and the goals and objectives of our study, the study included patients with neuropathic and neuro-ischemic forms of diabetic foot syndrome and with 3rd degree of foot damage according to Wagner [35].

In the main group, 25 (34.7%) patients were diagnosed with a neuro-ischemic form and 13 (18.1%) with a neuropathic form of diabetic foot syndrome, in the

comparison group, 23 (30.6%) with a neuro-ischemic form, and 11 (16.6%) with a neuropathic form.

The study methods were comprehensive and included: a standard survey taking into account the anamnesis of complaints, anamnestic data and physical examination. When examining the lower extremities, attention was paid to the colour of the skin, the presence of oedema, the temperature of the skin, and the presence of hyperkeratosis and deformities. Upon admission and in dynamics, the area and depth of the ulcerative defect were measured, and the presence of local signs of infection was recorded.

Laboratory research methods consisted of determining: the level of glucose in capillary blood was determined using standard test strips on the glucometer "Glucotrend" (Boehringer Mannheim Roche) (Austria); the level of glycated haemoglobin was determined on the DCA-2000 device by latex inhibition of immunoagglutination using the Hemoglobin Ale Reagent kit.

All patients underwent an immunological study of the level of pro- and anti-inflammatory cytokines (IL-8 and TGF- β) in the blood serum and exudate of wound discharge of ulcerative defect before and after treatment. The material was taken from the purulent-necrotic focus with 1.0x1.0 cm filter paper, which was then placed in a 1.5 ml Eppendorf tube in 100 μ l of sterile saline, after 30 minutes the filter paper was removed and the contents of the tube were frozen for further storage for a month.

Determination of the level of cytokines was carried out by enzyme-linked immunosorbent assay using test systems manufactured by BIOSOURCE (Belgium). Test systems are microplates coated with antibodies to the antigen - the cytokine structure under study, in our case IL-8 and TGF- β .

In patients with ulcerative defects with rough hyperkeratosis edges, the wound was cleaned mechanically with a scalpel, then the ulcerative defect was washed with a liquid antiseptic (0.5% solution of Dioxidine, 0.01% solution of Miramistin, or solution of Chlorhexidine). After treatment of the ulcerative defect, an atraumatic bandage was applied to the wound. Since the patients we observed were in the first stage of the wound process, dressings with water-soluble ointments (Levomekol or Dioxycol) were used in the patients of the comparison group. Patients of the main group underwent dressings with Superlymphoma, which is a standardized complex of cytokines, among which the activity of IL-1, 2, 6, tumour necrosis factor- α (FNO- α), factor inhibiting phagocyte migration, TGF- β was determined.

In our study, we used lyophilized Superlymph powder: 1 ampoule of dry matter of the drug was diluted in 2 ml of 0.9% sterile saline solution and applied locally to the wound in the form of applications 1 time per day for 7 days.

The criteria for evaluating the effectiveness of therapy were clinical (dynamics of subjective and neurological symptoms, eradication of pathogens from the focus of inflammation, dynamics of the wound process and local status, length of hospital stay), laboratory (changes in the peripheral blood formula, changes in biochemical parameters) and immunological parameters (cytokine levels). Evaluation of the effectiveness of treatment was carried out immediately after treatment.

Statistical data processing was carried out using the statistical package of the Statistica vers program. 6 and MS EXCEL spreadsheets version 2003 using standard parametric methods of variation statistics.

RESULTS AND DISCUSSION

Correction of carbohydrate metabolism was one of the main tasks of the therapy carried out in both clinical groups. The prescribed adequate insulin therapy made it possible to significantly ($p < 0.01$) reduce the level of glycated haemoglobin and fasting blood glucose in both clinical groups, blood glucose after meals in the comparison group did not significantly decrease. Comparing these indicators after treatment, we found that in the main group, these indicators significantly decreased more than in the comparison group. In order to exclude the positive effect of diabetes mellitus compensation on the dynamics of the treatment of patients in the main group and to equally compare the effectiveness of the therapy in both study groups, regardless of the indicators of carbohydrate metabolism, we took from the main group of patients who, after treatment, did not differ from the corresponding values of patients in the comparison group. It was in these patients of the main group that we evaluated clinical, laboratory and immunological parameters over time. There were 27 such patients in the main group.

As a result of the treatment, most patients of the main and comparative groups noted an improvement in well-being - a decrease and disappearance of pain in the area of the ulcerative defect, the disappearance of paresthesia, a decrease in the frequency of muscle cramps, an increase in endurance when walking. We did not find any significant differences in the dynamics of objective symptoms in the studied groups.

When comparing the time of relief of pain, normalization of body temperature and relief of acute phenomena in the group of patients in whom Superlymph was used, these indicators were significantly ($p < 0.01$) stopped faster than in the comparison group.

In the study of the neurological status in dynamics, a significant ($p<0.05$) improvement in almost all reflexes and types of sensitivity was noted in patients of both clinical groups. However, after treatment, pain sensitivity decreased, and vibration sensitivity increased significantly ($p<0.01$) in patients of the main group than in patients in the comparison group. Moreover, it should be noted that the threshold of vibration sensitivity before treatment in both groups was lower than the age norm (the lower limit of the norm of 60-70 years is 4.0 conventional units), and after treatment in the main group, the threshold of vibration sensitivity approached the norm of this age group - 3.8 ± 1.0 conventional units, while in the comparison group, the vibration sensitivity index remained below the norm of - 2.8 ± 1.1 conventional units.

Changes in the feet, such as dryness and atrophy of the skin, hyperkeratosis, deformity of the foot and toes, thickening of the nail plates, which were detected during an external examination of the feet, persisted after the therapy in most patients of the observed groups, as they are persistent and irreversible changes. Edema of the feet in patients of the main and comparative groups decreased significantly ($p<0.05$). However, in the main group, the swelling of the feet observed in 11 (40%) cases disappeared completely, while in the comparison group, the edema observed before treatment in 15 (44%) patients persisted after treatment in 8 (23.5%) patients ($p<0.01$).

In the analysis of clinical and laboratory signs of intoxication in both clinical groups after treatment, significant ($p<0.05$) differences in the level of leukocytes, stab neutrophils, and erythrocyte sedimentation rate were revealed.

In the main group, there was a normalization of all parameters, in the comparison group, there was a normalization of the level of leukocytes and the erythrocyte sedimentation rate. Local cytokine therapy led to a decrease in the overall level of intoxication.

After the therapy, according to bacteriological studies, eradication of pathogens was achieved in 22 (81.5%) patients treated with Superlymph and in 18 (53%) patients in the comparison group.

In the study of seeding from ulcerative defects after therapy, 4 types of microorganisms were isolated in the study group in 5 (18.5%) patients versus 5 microorganisms in 16 (47%) patients in the comparison group. However, we did not observe significant differences in the quantitative value of each of the identified microorganisms after treatment in the main group and the comparison group.

When analyzing the X-ray examination of the feet and Doppler ultrasound of the arteries of the lower extremities, we did not reveal changes in the indicators of

these studies after the course of treatment in any of the clinical groups, from which it follows that Superlymph, being an immunomodulator, does not affect the remodeling of bone structures and stenotic changes in the arteries of the lower extremities in the neuro-ischemic form of diabetic foot syndrome.

The area of the wound and the depth of the ulcerative defect after treatment were significantly ($p < 0.05$) smaller in patients of the main group.

To analyze the effectiveness of local cytokine therapy with Superlymphomas, we studied the dynamics of the wound process in the patients we observed before and after the course of therapy. In patients in the comparison group, wound healing was slower compared to the study group.

The dynamics of the wound process in the main group were more intense. Apparently, under the influence of exogenous cytokines that make up Superlymph, there is a change in the intrinsic cytokine background of tissues, a local cytokine cascade is launched, followed by an increase in the proliferation of T and B lymphocytes, their migration from the lymphatic system into the blood and into the focus of inflammation, as well as activation of migration and fixation of macrophages in the focus of inflammation and an increase in their phagocytic activity [5]. The complex of cytokines included in Superlymph stimulates collagen synthesis, a proliferation of fibroblasts, endothelial cells, and nerve formations. All of the above determines the local and less pronounced nature of the inflammatory response [26]. 8-10 minutes are enough to connect cytokines that are part of Superlymph with receptors of target cells, thus, cytokines and growth factors of the drug do not have time to be inactivated by protein kinases of wound discharge exudate [34]. All of these properties of Superlymph allowed us to achieve faster positive dynamics of the wound process.

In the group of patients receiving Superlymph, there was a significant decrease in the pro-inflammatory cytokine IL-8 and a significant increase in the anti-inflammatory cytokine TGF- β . According to the correlation analysis in the main group, a negative correlation relationship ($r = -0.81$, $p < 0.05$) between the levels of IL-8 and TGF- β after treatment was revealed. This correlation was not found in the comparison group.

When correlations were detected between the level of cytokines studied and the levels of leukocytes, neutrophils, and erythrocyte sedimentation rate after treatment, correlations were detected only in patients of the main group. A positive relationship was found between the level of IL-8 and the level of leukocytosis: $g = 0.8$, $p < 0.05$. and also revealed a negative correlation between the level of TGF- β the levels of leukocytes, neutrophils and erythrocyte sedimentation rate: $g = -0.76$, $p < 0.05$ and $g = -0.47$, $p < 0.05$ and $g = 0.83$, $p < 0.05$, respectively.

When evaluating the effectiveness of treatment, we noted good results, satisfactory and unsatisfactory results. With the traditional method of treatment of patients with diabetic foot syndrome, a good treatment result can be achieved only in 38.2% of patients, at the same time, as with the use of Superlymph, this effect can be obtained in 71% of patients. With the use of Superlymph, it was possible to reduce by 2.3 times the number of patients with unsatisfactory treatment results compared to traditional treatment.

CONCLUSION

In patients with diabetic foot syndrome, changes in the local cytokine status in the exudate of the wound discharge are presented in the form of an increase in the pro-inflammatory cytokine IL-8 and a decrease in the anti-inflammatory cytokine TGF- β . As a result of the study, positive correlations were established between the duration of diabetes mellitus, the level of glycated haemoglobin and the initial level of IL-8 and negative correlations between the duration of diabetes mellitus, glycated haemoglobin and the initial level of TGF- β . At the same time, the analysis of data on the content of the studied cytokines in the exudate of wound discharge did not reveal statistically significant differences in cytokine levels in neuropathic and neuro-ischemic forms of diabetic foot syndrome.

Superlymphoma topical therapy helps to increase the level of anti-inflammatory (TGF- β) and reduce the level of pro-inflammatory (IL-8) cytokines in the exudate of wound discharge in patients with diabetic foot syndrome. In this connection, after treatment in the group of patients receiving Superlymph, a negative correlation between the levels of IL-8 and TGF- β was revealed. This contributes to more rapid normalization of intoxication parameters, intensive positive dynamics of the wound process, reduces the length of hospital stay from an average of 26 to 20 days, and contributes to the eradication of bacterial flora from the focus of inflammation.

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