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DEVELOPMENT OF DIAGNOSTIC CRITERIA FOR WOUND PROCESS PHASES IN EXPERIMENTAL ANIMALS WITH DIABETES MELLITUS AND SYSTEMIC INFLAMMATORY REACTION SYNDROME

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Abstract: The optimal model for calculating the diagnosis of the phase of the course of the wound process, complicated by the syndrome of systemic inflammatory response against the background of diabetes mellitus, was selected. The developed mathematical model was the basis of the software module: a method for diagnosing the phase of the wound process complicated by the systemic inflammatory response syndrome in experimental animals with diabetes mellitus. It allows diagnosing the phase of the course of the wound process, predicting the likelihood of a generalization of the pathological process, and can be used as a criterion in choosing the optimal method for local treatment of wound infection, thereby reducing the average duration of the hospital stage of complex treatment.
Keywords: Diabetes, pathological process, software module, purulent diseases of soft tissues.

Relevance. The last fifty years have seen a steady increase in the prevalence of diabetes mellitus worldwide (11,19). The problem of treating purulent diseases of soft tissues, remaining relevant throughout the history of mankind, under conditions of a high incidence of diabetes mellitus, is becoming increasingly important both clinically and socially (3,4).

Scientists have long studied the pathogenetic factors that affect the course of the wound process in patients with diabetes mellitus (16). It has been proven that diabetes mellitus creates favorable conditions for the development of a wound infection process. At the same time, the infectious process itself negatively affects the course of diabetes mellitus, by suppressing insulin deficiency and, accordingly, provoking the development of metabolic acidosis. Thus, a close relationship is formed that enhances the aggressive aspects of the disease (1,5).

Along with this, the course of the purulent-inflammatory process under conditions of progressive metabolic acidosis is often complicated by the accelerated generalization of the infection. A systemic inflammatory response syndrome develops, which "randomly" engages the body's immune system (2,7,8,20).

And today, the study of pathogenetic factors in the development of the wound process, complicated by the syndrome of systemic inflammatory response in patients with diabetes mellitus, becomes paramount, determining the high relevance of this problem (10,18,19).

The protracted course of regenerative processes of wound infection in patients with diabetes mellitus is the starting foundation for the development of systemic inflammatory response syndrome and sepsis, which often does not allow to reduce the duration of the inpatient treatment period (13,14,17). It requires constant monitoring of both the course of the wound process and the general manifestations of a possible generalization of the infection. This, in turn, leads to an increase in bed days and a high risk of hospital infection (2,6,9,12,15). The solution to this problem is possible by optimizing the methods of local wound treatment, based on objective methods for assessing the phases of the inflammatory process.

The presented data indicate the feasibility of conducting studies on a more in-depth and detailed study of the effect of various methods of local complex treatment of wound infection in patients with diabetes mellitus complicated by the systemic inflammatory response syndrome, which would reduce the number of adverse and fatal outcomes of the disease and reduce the duration of inpatient treatment.

Purpose of the study: development and experimental substantiation of the effectiveness of diagnostic criteria for the phases of the course of the wound process in experimental animals with diabetes mellitus and systemic inflammatory response syndrome.

Material and methods.

Experimental studies were carried out on 280 mature white Wistar rats weighing 180–280 g, of both sexes, without external signs of the disease, which underwent a 10-day quarantine in a vivarium. All animals were divided into 3 large groups and 3 subgroups, consisting of standard series of experiments. Accordingly, each series of experiments corresponded to a certain model of the pathological process and was numbered by us with Roman numerals. I series of experiments - control, consisted of animals with the course of the wound process without the introduction of an infectious agent. In this series of experiments, the skin, subcutaneous tissue and superficial fascia were opened in the back area of animals under superficial inhalation anesthesia, followed by the removal of a soft tissue flap measuring 1.5x1.5 cm. This manipulation was recorded by us as a stage of surgical treatment. The wound was left open using the appropriate drug as a therapeutic agent according to the established objectives of the study. II series of experiments - comparative-1, consisted of animals during the wound process with the introduction of an infectious agent into soft tissues. In this series of experiments, animals under surface inhalation anesthesia were injected subcutaneously at 5 points on the animal's back with 3–4 ml of a 30% suspension of the animal's autocal diluted with a 10% solution of calcium chloride. After the manifestation of the inflammatory process, which occurred on the 3rd–5th day after the administration of the autocal suspension, CHO with complete necrectomy was performed. The wound was left open using the appropriate drug as a therapeutic agent according to the established objectives of the study. III series of experiments - comparative-2, consisted of animals with the course of the wound process with the introduction of an infectious agent into soft tissues, followed by the development of SIRS. Modeling was carried out according to the method developed by A.O. Okhunov. According to the conditions of this

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development, animals on an empty stomach under ether anesthesia for 2 days were injected intraperitoneally with antilympholin-Kr at a dose of 0.03 mg per 100 g of animal weight. On the 3rd day, 3–4 ml of a 30% suspension of the animal's autocal diluted with a 10% solution of calcium chloride was injected subcutaneously at 5 points on the animal's back. After the manifestation of the inflammatory process, which occurred on the 5th–7th day after the administration of the autocal suspension, CHO with complete necrectomy was performed. The wound was left open using the appropriate drug as a therapeutic agent according to the established objectives of the study.

IV series of experiments - the main one, consisted of animals with the course of a wound process with the introduction of an infectious agent into soft tissues, followed by the development of SIRS on the background of diabetes mellitus with diabetic microangiopathy. Modeling was carried out according to the method developed by A.O. Okhunov. According to the conditions of this development, animals on an empty stomach under ether anesthesia were intravenously injected with 100–110 mg/kg of the drug doxorubicin in a 0.9% solution of sodium chloride, and 48 hours after the administration of doxorubicin, once a day for 3 days, retroperitoneally administered 0.2 -0.4 ml per 100 grams of animal weight of 70% sorbitol solution. After clinical and laboratory ascertaining the development of diabetes mellitus (hyperglycemia, glucosuria), antilympholin-Kr was administered intraperitoneally for 2 days under ether anesthesia at a dose of 0.03 mg per 100 g of animal weight. On the 3rd day, 3–4 ml of a 30% suspension of the animal's autocal diluted with a 10% solution of calcium chloride was injected subcutaneously at 5 points on the animal's back. After the manifestation of the inflammatory process, which occurred on the 3rd–5th day after the administration of the autocal suspension, CHO with complete necrectomy was performed. The wound was left open using the appropriate drug as a therapeutic agent according to the established objectives of the study.

Animal subgroups were formed and named according to the type of local wound infection treatment used.

Experimental animals were subjected to a comprehensive clinical examination using modern clinical, biochemical and instrumental research methods.

As express methods for local assessment of the state of the wound process and signs of inflammation intensity were: hyperemia, edema and infiltration of tissues in the wound area, the amount and nature of wound discharge, the intensity of necrolysis, the timing and degree of wound epithelization and scar tissue formation. Important research methods were the assessment of the area and the level of the depth of the spread of the purulent-inflammatory process of soft tissues. Depth was assessed according to the D.H. Ahrenholz, and prevalence - according to the classification of S.V. Goryunov. After CHOGO, the course of the wound process was carried out by determining according to the method of L.N. Popova: the area of the wound, the percentage of reduction in the area of the wound and the rate of wound healing.

The presence of septic complications was identified based on the criteria proposed by the Chicago Consensus Conference. For differentiation, we adhered to the following specific clinical concepts: systemic inflammatory response syndrome, sepsis syndrome, severe sepsis, and septic shock. In experimental animals, to detect clinical signs of SIRS, respiratory movements were visually counted in 1 minute. The pulse rate was determined by the number of heartbeats in 1 minute. The rectal temperature was measured and the number of leukocytes in the blood was counted with the determination of the number of neutrophils.

Special laboratory research methods went beyond the general approved standards and were originally carried out for scientific research. The concentration of cytokines (IL-1b, IL-6, TNF-α) in blood serum was determined by enzyme-linked immunosorbent assay using a set of reagents of the test system manufactured by Cytokines LLC (Russia).

The material for microbiological studies was purulent exudate taken from the deep sections of the wound immediately after opening the pathological focus and in the dynamics of the treatment.

Morphological studies were carried out in experimental animals and included histological and morphometric studies. Morphometric parameters were: areas of stromal edema, dermal vessels and granulation vessels; diameter of the vessels of the dermis and granulation; the number of wound fibroblasts, granulocytes, lymphocytes and macrophages. Research of laboratory animals was carried out according to the general design. At the same time, in group No. 1 of experimental animals, it was planned to study the clinical, laboratory and morphofunctional dynamics of the course of the wound process on days 1, 3, 7, 14, and 28 after CHO. As a therapeutic agent in all four series of experiments, a dressing soaked with a 3% hydrogen peroxide solution was used.

The purpose of the ongoing research in experimental animals in the second group was aimed at assessing the effectiveness of the impact of various methods of local treatment on the dynamics of the course of the wound process. At the same time, a group consisting of 3 subgroups included conducting studies to evaluate the effectiveness of Oflomelide, Sulfargin and Altrazeal in all series of experiments on days 1, 3, 7, 14 and 28 after CHO.

To develop a treatment and diagnostic algorithm for the optimal method of local treatment of wound infection, group No. 3 was created, in which studies were also carried out, based on a modified method for assessing the phase of the course of the wound process. Studies, as well as in other groups, were carried out on days 1, 3, 7, 14 and 28 after CHO.

To evaluate the results of the treatment of a wound infection complicated by a systemic inflammatory response syndrome in patients with diabetes mellitus, we used a modified method proposed by the Republican Center for Purulent Surgery and Surgical Complications of Diabetes Mellitus of the Ministry of Health of the Republic of Uzbekistan. The following criteria were distinguished in the evaluation structure:

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1. The wound healed completely by self-scarring, the anatomical structure of tissues and ability to work were completely restored;

2. The wound healed after plastic surgery, the anatomical structure of the tissues was restored within the limits of cosmetic defects and partial recovery;

3. Wound healing occurred after repeated necrectomy followed by plastic surgery, there is a rough deforming scar, activity was restored only within self-service;

4. Preservation of the inflammatory process in the wound even after repeated CHO, the integrity of the wound is not restored, the ability to work is completely lost;

5. Death of the experimental animal.

Correlation significance and predictive value of the obtained data were determined by the method of R. Fletcher.

Results and its discussion. The clinical picture of the dynamics of the course of the wound process with various variants of experimental models is shown in Figure 1. During a local examination, we stated the following indicators: the timing of the disappearance of edema in the peripheral part of the wound; the timing when the wound was cleared of necrotic tissue; the time when it was already possible to visualize the presence of granulation tissue; the time when signs of epithelialization of the wound edges appeared. The minimum terms of wound transformation were noted by us in the 1st series of experiments, while the maximum - in the 3rd and 4th.

Since the first series of experiments was characterized by the absence of an infectious provocation, the wound remained macroscopically clean throughout the study. Granulation already appeared on the 2.7±0.6 day, and marginal etithelialization - on the 3.4±0.8 day of the postoperative period. In the main series of experiments, peripheral tissue edema persisted up to 9.8±1.3 days of the postoperative period ($p<0.05$). Cleansing of the wound from necrotic tissues (including secondary ones) occurred only on 13.8±4.3 days of observation ($p<0.05$), which of course is not comparable with the control series of experiments. Granulation in the wound appeared 16±2.6 days later than in the control ($p<0.05$). Accordingly, the beginning of the marginal epithelialization of the wound was registered by us only on day 25.9±3.7 of the postoperative period ($p<0.05$). We deliberately do not dwell on the indicators in the II and III series of the experiment, since they were of an intermediate nature between the control and main groups, which, in fact, was expected. Of the total number of animals in this block of experiments, the incidence of SIRS manifestations was 56% of cases.

Such a high value of this indicator is due to the totality in the analysis of all the studied groups. Nevertheless, the number of animals with signs of SIRS2 or more was 47.5%. The number of animals with purposeful modeling of SIRS (III and IV series of experiments) was 43.7%.

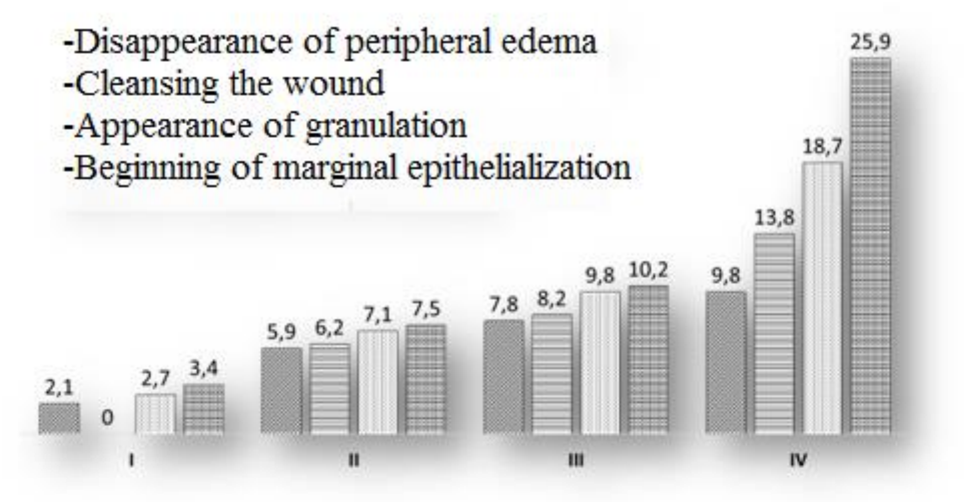

Figure 2. Dynamics of ongoing visual changes in animals with various experimental models of wound infection

Among the animals of series IV, signs of SIRS were registered by us in 98% of cases. At the same time, out of 36 animals with SIRS4, in 75% of cases there were animals of the IV series of experiments.

Thus, the analysis of the distribution of the frequency of registration of SIRS showed that the selected various experimental models of wound infection are reliable in terms of clinical and laboratory signs of the course and can be used in further studies.

A microbiological study of the wound of all animals in the dynamics of the development of wound infection showed that, on average, on the 1st day of the experimental experiments, the number of microorganisms was the highest - 68.6x107±15.8 CFU/g. In the dynamics of the experiments, already on the 14th day of the research, a more than 2-fold decrease in this indicator was noted, both in the number of microorganisms and their colonies. Among the series of experiments on the 1st day of experiments, the highest contamination of the wound was registered among animals of series III and IV (92.4x107±25.8 CFU/g ($p<0.05$) and 89.9x108±17.6 CFU/g ($p <0.05$) respectively).

It is noteworthy that even on the 28th day of observation, the microbial contamination of the wound of the animals of the IV series of experiments still remained high, both above the average value (3.5 times) and above all other comparative values (27.8 times compared with II and II). 10.4 times compared with group III, respectively) and control (compared with 14 days of experiments) groups ($p<0.05$). You should also focus on the number of degrees of microbial contamination of the wound. The maximum degree at the level of 107-108 was noted by us in III and IV series of experiments, that is, in animals with a model of the septic course of the inflammatory process.

The dynamics of the level of cytokines in the blood in animals of the first series of experiments did not reveal any significant changes. All indicators of cytokines, including their average value, were within normal limits and any increase or decrease in the digital value did not have a fundamental deviation.

The maximum value in relation to IL-1b and IL-6 was noted on the 28th day of observation. The same kind of changes were registered by us with TNF-α on the 3rd day after CHO. The average value of all cytokines in dynamics after CHO in animals of the first series of experiments varied from 3.0±0.4 pg/ml to 4.3±0.8 pg/ml. In the second series of experiments, the average concentration of pro-inflammatory cytokines was high during 1–7 days of the process dynamics. The peak value was on the 1st day of the study with a gradual decrease on the 7th day, that is, the dynamics of changes corresponded to the dynamics of the process.

Among the pro-inflammatory cytokines, TNF-α distinguished itself, the level of which varied from 9.3±0.5 pg/ml ($p<0.05$) to 22.4±1.6 pg/ml ($p<0.05$) for 1 -14 days postoperative period. IL-1 decreased already starting from the 3rd day of the study by 2.7±0.2 pg/ml ($p<0.05$), and IL-6 - from the 7th day by 12.6±1.2 pg/ml ($p <0.05$).

III series of experiments, where the complication of wound infection in the form of SIRS was purposefully modeled, the average value of all studied pro-inflammatory cytokines was higher than the values of the control series of experiments. Already on the 1st day of research, their level exceeded the indicators of the control series by 11.3 times ($p<0.05$), and the indicators of the II series of experiments - by 2.6 times ($p<0.05$). It should be noted that the 3rd day of the postoperative period also had a significant difference between the III series of experiments and I-II series. The difference was manifested in an increase in the mean value by 15.4 ($p<0.05$) and 3.6 times ($p<0.05$). This confirms the existence of a connection between the development of cytokinemia and the presence, in this case, of bacteriological presence in the inflammatory process.

Even on the 28th day of the postoperative period in the III series of experiments, we did not find any hint of the normalization of the level of cytokines. IL-1 was 1.6 times higher than the control values ($p<0.05$), IL-6 was 9.1 times higher ($p<0.05$), and TNF-α was 1.4 times higher ($p<0.05$). 0.05).

In animals of the IV series of experiments, the level of cytokines was increased for all the studied cytokines throughout the entire experiment. The average value of cytokinemia on the 1st day of the postoperative period exceeded the control values by 25.5 times ($p<0.05$). On the 3rd day of observation, there were no significant changes in the dynamics. Only starting from the 7th day of the course of the postoperative period, on average, there was a decrease by 1.6 times ($p<0.05$) compared with the previously studied period. Meanwhile, in relation to the I series of experiments, in IV this indicator exceeded its values by 16.3 times ($p<0.05$). Throughout the studies in the IV series of experiments, the level of IL-6 was the leader among pro-inflammatory cytokines, and its dispersion compared to other pro-inflammatory cytokines was paramount, exceeding IL-1 by 2.5 times ($p<0.05$) and TNF-α – 2.9

times ($p<0.05$). On the 1st day of the study, the dispersion of pro-inflammatory cytokines was distributed in descending order according to the scheme IL-6/ IL-1/ TNF-α. Starting from the 3rd day of the postoperative period, the scheme changed, acquiring the pattern of IL-6/TNF-α/IL-1. And although the order of their dispersion changed, nevertheless, in numerical terms, all the studied pro-inflammatory cytokines exceeded both the control values and the values of the comparative experimental groups. The increase in comparison with the control series of experiments on the 28th day of observation of the pro-inflammatory cytokine IL-1 was 6.8 times ($p<0.05$), IL-6 - 18.7 times ($p<0.05$), TNF-α – 6.9 times ($p<0.05$).

Thus, a comparative assessment of the dynamics of changes in the level of pro-inflammatory cytokines in animals with various experimental models of wound infection made it possible to determine the important role of these indicators as criteria for differentiating the type and duration of the inflammatory process. Modeling of wound infection against the background of diabetes mellitus and complications in the form of SIRS influenced the change not only in the numerical change of these indicators, but also in the nature of their dispersion redistribution. This indicates the reliability of both the selected options for modeling the pathological process, and the possibility of using these indicators in predicting purulent-septic complications of the wound process.

In general, summing up the analyzed clinical and laboratory manifestations of wound infection, it can be stated that the level of pro-inflammatory cytokines, the number of signs of SIRS and the microbial contamination of the wound should be taken into account when developing diagnostic criteria for the phases of the wound process. To assess the effectiveness of these criteria, a more in-depth morphological and morphometric study of the wound process in dynamics after CHO is required.

Morphological and morphometric characteristics of the course of the wound process in various types of wound infection on the 1st day after modeling in II, III and IV series of experiments looked as follows. Over the entire wound surface there are overlays, which were due to fibrin. The entire area of the connective tissue, which was examined at the bottom of the wound, was loosened, and the tissue itself was filled with macrophages, leukocytes according to the type of infiltration. It was in this area that a pronounced swelling of the tissues was determined. The blood vessels were dilated. You can see areas of hemorrhage around the dilated vessels, most likely due to diapedesis. In the study of deep tissues along the periphery of the wound surface, we stated the presence of edema. On the 3rd day of research, in a series of experiments, differences appeared in the morphological structure of tissues. In particular, in the first series of experiments, the wound was infiltrated with neutrophils, but under the infiltration one can see edematous granulation tissue, which was of an emerging character. In the second series of experiments, fibrin completely covered the wound surface.

Deeper lying tissues were represented by early granulation, which, unlike the previous series of experiments, had a pronounced infiltration of leukocyte cells. These cells had polymorphic nuclei. Adipose tissue around the wound was distinguished by the presence of pronounced edema. In the third series of experiments, it was found that the dermis was stratified. At the same time, a pronounced infiltrate is noted between its layers. The infiltrate contains a large number of leukocytes with a different morphological picture of the nuclei. Swelling of the tissues occurs due to the difficulty in the outflow of lymph, which is manifested by the expansion of the lymphatic capillaries. Deep tissue layers are also edematous and also have stratification due to edematous infiltration. In the IV series of experiments, in fact, all layers of the tissue were filled with a pronounced infiltrate, which was of an inflammatory nature and was abundantly saturated with neutrophils. The inflammatory process was destructive in nature, so a similar transformation was noted throughout the depth of the tissues with the transition to the muscles. On the 7th-14th day in the first series of experiments, the process of epithelization is actively developing, the wound is without areas of necrotic tissues.

In the second series of experiments, collagen appears around the wound surface. Over the entire surface of the wound cover, there is an activation of the growth of granulation tissue. However, in some areas, fibrin is still superimposed on the growth tissue. Under the layers of epithelialized areas of the wound, moderate edema is noted.

In the III series of experiments, we did not reveal any special dynamics of the morphological picture. The granulation tissue is also edematous. In this case, the edema also spreads to the layers of fatty tissue around the wound.

In the IV series of experiments, tissue necrosis is determined in the wound. The vessels are filled with blood clots. Their diameter is sharply reduced. The tissue around the wound is sharply edematous, infiltrated. Edema and infiltrate reaches the muscles. The latter with areas of necrotic change

The average value of the indicators characterizing the morphological picture of the course of the wound and wound infection, with the cumulation of indicators between the control, comparative and main groups, revealed the ambiguity of changes. However, when assessing the cellular composition of the wound imprints in the dynamics of the postoperative period (Table 4), already on the 1st day of the postoperative period, one can note the predominant number of granulocytes, which accounted for more than half of the total volume under study in this period.

A targeted study of the dynamics of this indicator reflected a decrease in its number, already starting from the 3rd day of the postoperative period, and from the 7th day this change began to acquire a significant value.

An insignificant change, in the total value, was characterized by the level of lymphocytes. And only on the 28th day of the postoperative period did it reach a significant value, decreasing compared to the 1st day of the study by 1.4 times ($p<0.05$).

In general, the dynamics of changes in the picture of the cellular composition of the wound infiltrate in the postoperative period, even under the condition of their average value, was characterized by a well-known pattern. However, when assessing the changes in these indicators in the dynamics of the postoperative period in various studied groups of experimental animals, it revealed a very differentiated picture. The peak value in the control series of experiments in relation to fibroblasts was on the 14th day of the postoperative period, while for granulocytes - on the 3rd day. Against this background, there was a progressive decrease in the number of lymphocytes and macrophages in all periods of the experiments in animals of this series.

The group of the main series of experiments was characterized by a depressive value of the number of fibroblasts, lymphocytes, and especially macrophages, both in general and in the early postoperative period. The level of fibroblasts on day 1 of the postoperative period in the main series of experiments was 1.5±0.2 times lower than the control values ($p<0.05$). At the same time, on the 14th day (the deadline for observations for the control series of experiments) in the main series of experiments, the level of fibroblasts in the wound infiltrate was 1.7±0.3 times lower ($p<0.05$).

When assessing the change in the level of granulocytes, it should be noted the same dynamics in reducing the number of indicators. When comparing the corresponding terms of a series of experiments, the decrease was noted in almost the same proportion (1.1±0.3%; $p<0.05$). However, in percentage terms, the number of granulocytes in the main series of experiments on the 14th day of the study was higher than the control values by 25.3±2.5% ($p<0.05$). Since in the control series of experiments by the 28th day of the study the wound was practically closed, a comparison of the main group was carried out with II and III series of experiments. At the same time, the level of granulocytes on the 28th day of the experiments exceeded by 38.9±7.8% ($p<0.05$) and by 11.9±0.95% ($p<0.05$), respectively. In general, in the main series of experiments, the level of granulocytes was close to series II. The difference was not significant, which indicates the similarity of pathological processes between these groups.

Another characteristic dynamics for the main series of experiments was the relative stability of the level of lymphocytes and macrophages in the imprints of the wound infiltrate. However, in contrast to the control series of experiments, even on the first day of the experiments, there was a low value of macrophages in the wound, actually by 12.1±1.8% ($p<0.05$). At the height of the wound infection on the 7th day of the postoperative period, the level of macrophages in the infiltrate in the main series of experiments was 3.6±0.8% than in the control ($p<0.05$).

In general, the minimum value of macrophages in the wound infiltrate of animals was noted on the 28th day of the postoperative period in the III series of experiments (1.1±0.08%; $p<0.05$). At the same time, the minimum value of lymphocytes in the wound infiltrate accounted for the main series of experiments (4.1±1.0%; $p<0.05$).

Morphometric study of wound biopsy specimens from animals of different series, in the average value, showed the following: stromal edema decreased the most, starting already from the early postoperative period, reaching its minimum value on day 28 (from 20.2±3.8% to 9. 6±1.7%, respectively; $p<0.05$). At the same time, a decrease in this indicator was noted by 2.1±0.4 times ($p<0.05$).

The area of the vessels of the dermis (as well as their diameter in other respects) on the 28th day of experimental studies decreased (almost 2.5 times). There was a significant increase in the area of granulation vessels and their diameter (11.8±2.4 times ($p<0.05$) and 3.3±0.8 times, respectively; $p<0.05$). It should be noted that these indicators changed significantly, starting from the 3rd day of the study, whereas in the previous case, such changes were noted only on the 28th day of the postoperative period.

In the main series of experiments, within the subgroup itself, significant changes were noted only in relation to the volume of the dermal vessel area. There was a progressive decrease in this indicator on the 28th day of the postoperative period (by 2.5 times) compared with the 1st day of observation. According to other indicators of the morphometric picture, compared with the intragroup picture, no significant changes were noted. The pathological process seems to have stopped in dynamics, without leading to any significant dynamic shifts. Meanwhile, in a comparative analysis between the control and the main series of experiments, changes of a mirror-opposite nature should be distinguished. In the control series of experiments, stromal tissue edema increased, reaching its maximum value already on the 7th day of the postoperative period. In the main group, in the presence of an initially high value of this indicator, there was a smooth, not significant decrease over 7-14 days of the postoperative period. However, in relation to the control series of experiments, this was very distinguishable. It should be noted that, in contrast to the control series of experiments, in the main one, we did not find indicators characterizing the nature of granulation on days 1-3. This process began to form only starting from the 7th day of the postoperative period. In the III series of experiments, this trend was noted by us on the 1st day of the postoperative period.

The morphometric study confirmed the role of the experimental model of diabetes mellitus in the protracted course of wound infection. An important role in this process should be attributed to the presence of diabetic angiopathy and, of course, the initial decrease in the protective properties of the body against the background of SIRS.

Planimetric studies showed that the average value of the area, in the dynamics of studies, significantly decreased from 333.0±1.5 mm2 to 131.9±0.9 mm2 ($p<0.05$). Progress in reducing the area of the wound was recorded by us on the 14th day of observation (by 1.7 times compared with day 1). It is noteworthy that the decrease in the percentage of the area of the wound surface, which amounted to only 0.8±0.09% on day 1, increased to 68.9±1.1% on day 28 of the experiments ($p<0.05$). The rate of wound healing averaged 2±0.1% per day. At the same time, the peak value of this indicator fell on the 14th day of experimental studies (5.2±1.2% per day; $p<0.05$). And although the rate of wound healing on the 28th day of experimental studies was 1.5±0.5% per day, nevertheless it was slower than on the 3rd day of the course of the wound process (1.7±0.4% per day; $p<0 .05$).

Randomization of the studies revealed a highly differentiated picture of the wound healing process (Table 8). It should be noted that in group I of the series of

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experiments, where the wound was without infection, the healing process was completed earlier than the last period of the experiments. At the same time, it should be emphasized that when assessing the rate of wound healing, the possibilities of analysis were only starting from the 3rd day of the experiment. Day 0 of the dynamics was noted by us as the period after the completion of CHO in order to ascertain the differentiated volume of surgical intervention.

The results showed that the volume of CGO in the animals of the main series of experiments significantly exceeded that value than in the control series of experiments. The area of the wound surface of animals with diabetic angiopathy against the background of signs of SIRS was 160±5.9 mm2 larger compared to series II ($p<0.05$) and 89.8±4.1 mm2 compared to series III ($p< 0.05$). This indicates the prevalence of the inflammatory process more in the main group and the need for more extensive necrectomy.

The control and comparative groups of experiments were characterized by an acceleration of the wound healing rate starting from the 14th day of experimental studies (from 5.4±1.1% per day to 7.6±0.9% per day; $p<0.05$). At the same time, this indicator in the main series of experiments did not exceed 0.6 ± 0.03% per day in all periods of the studies. The percentage of reduction in the area of the wound in the IV series of experiments increased by 31.7 ± 1.3 times, while the area of the wound surface itself decreased by only 57.3 ± 1.2 mm2, which was 12.7 ± 0.8% of the initial area of the wound surface ($p<0.05$).

The analysis and practical application of such a massive information block requires the development of a software model that can be easily implemented in practical healthcare in the future.

Based on the goal and objectives, we present the results of the development of objective criteria for diagnosing the phase of the course of a wound infection, which will serve as the basis for creating a therapeutic and diagnostic algorithm for the local treatment of purulent wounds in patients with diabetes mellitus against the background of SIRS.

The first stage in the performance of this task, due to the impossibility of conducting studies of this kind on patients, was the study of morphological, morphometric, cytological and microbiological parameters of experimental animals.

Correlation assessment of the indicators of the conducted studies was carried out depending on the series of the experimental model of the pathological process. However, it had certain distinguishing features.

In all series of experiments, the correlation values of the dynamics of the course of the wound process indicated an increase in their significance in a particular direction vector (direct or reverse). In particular, the rate of wound healing had a direct correlation with the number of fibroblasts on the wound surface ($R=0.732\pm0.012$; $p<0.05$) and a weak inverse correlation with the number of granulocytes ($R=-0.469\pm0.009$; $p<0.05$), lymphocytes ($R=-0.364\pm0.006$; $p<0.05$) and macrophages ($R=-0.298\pm0.007$; $p<0.05$) in the wound. At the same time, the main series of experiments had the most pronounced picture (R=-0.965±0.01; p<0.05), exceeding those of the control by 68.7% (p<0.05).

A direct dependence was also noted in relation to the percentage of the area of stromal edema of the wound (in series I R=0.590±0.014; p<0.05; in series II R=0.612±0.014; p<0.05; in series III R=0.718 ±0.009; p<0.05; and in series IV R=0.962±0.027; p<0.05) and to an increase in both the area of granulation vessels (in series I R=0.485±0.01; p<0.05; in series II R=0.598±0.01, p<0.05, in series III R=0.628±0.01, p<0.05, and in series IV R=0.931±0.01, p<0, 05) and to the diameters of granulation vessels themselves (in series I R=0.320±0.01; p<0.05; in series II R=0.774±0.01; p<0.05; in series III R= 0.918±0.01; p<0.05; and in series IV R=0.984±0.01; p<0.05). An inverse correlation was noted for changes in the diameter of dermal vessels (in series I R=-0.618±0.01; p<0.05; in series II R=-0.832±0.01; p<0.05; in series III R=-0.932±0.01; p<0.05; and in series IV R=-0.993±0.01; p<0.05), which, in all likelihood, was associated with scar formation.

The microbial contamination of the wound, noted in inverse correlation with respect to the rate of wound healing (on average R=-0.859±0.01; p<0.05), had a direct relationship with the number of granulocytes (on average R=0.732±0.01 ; p<0.05), lymphocytes (mean R=0.649±0.02; p<0.05) and macrophages (mean R=0.579±0.05; p<0.05) in the wound, and reverse correlation with the number of fibroblasts in the wound surface (on average R=-0.598±0.03; p<0.05).

The area of tissue stromal edema was inversely correlated with the dynamics of microbial contamination of the wound (in series I R=-0.461±0.02; p<0.05; in series II R=-0.598±0.03; p<0.05 ; in series III R=-0.624±0.02; p<0.05; and in series IV R=-0.843±0.02; p<0.05). A weak correlation was noted in relation to other indicators of the wound process in the control series of experiments, since, apparently, the absence of targeted introduction of microorganisms into the wound in this series of experiments affected. The growth of granulation tissue vessels was inversely correlated with the microbial contamination of the wound (on average, R=-0.318±0.02; p<0.05).

Thus, the correlation analysis between the analyzed indicators of morphological, microbiological, cytological, morphometric and planimetric studies made it possible to identify a significant pattern in changes in the course of wound infection and the objectivity of the data presented.

The analysis of static data allowed us to identify data that were similar in nature of significance and served as the foundation for the formation of the integration of indicators. These indicators can serve as data for the course of the wound process complicated by SIRS against the background of diabetes mellitus.

We took the least squares method as the basis for the formation of models that can differentiate the stages of the course of the wound process in diabetes mellitus complicated by SIRS. The statistical basis was composed of model parameters that imposed the condition that their effectiveness was not lower than the p<0.05 level according to the t-test. This allowed us, in turn, to develop a model for diagnosing the phase of the course of a wound process complicated with SIRS against the background of diabetes mellitus. At the same time, subject to the presence of a wound infection complicated by a syndrome of systemic inflammatory response against the background of diabetes mellitus, it has its own distinctive side, characterized by a more radical approach in CHO tactics. In this connection, it is logical to exclude the wound cleansing phase.

Morphological information, the results of clinical and laboratory analyzes - all of them confirm the peculiarity of the course of the wound process in this experimental model and, accordingly, define the phases as: 1) an active inflammatory process, with a probability of developing SIRS in 75% of cases; 2) passive inflammatory process, with a probability of developing SIRS in 50% of cases; 3) active regeneration, with a probability of developing SIRS in less than 25% of cases;

The characteristic changes were recognized as the closest in pathogenetic significance, first of all, pro-inflammatory cytokines and the number of signs of SIRS. Subsequently, the construction included data on the microbial contamination of the wound and the rate of wound healing.

Thus, we have selected the optimal model for calculating the diagnosis of the phase of the course of the wound process, complicated by the syndrome of systemic inflammatory response against the background of diabetes mellitus. The developed mathematical model was the basis of the software module "Method for diagnosing the phase of the wound process complicated by the syndrome of systemic inflammatory response in patients with diabetes mellitus." infections.

Conclusions:

1. The developed and experimentally substantiated model of diagnostic criteria for the phases of the course of the wound process makes it possible to diagnose the phase of the wound process, which makes it possible to correctly assess the course of the pathological process and optimize local treatment.
2. On the basis of the conducted studies, it has been proved that the use of diagnostic criteria for the phases of the course of the wound process leads to the correct approach to the choice of local treatment for wound infection, thereby reducing the average duration of the hospital stage of complex treatment.

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