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Immediate And Long-Term Outcomes Of The Treatment Of Patients With Purulent-Necrotic Complications Of The Diabetic Foot Syndrome With The Use Of Programmable Sanation Technologies.

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ABSTRACT

Diabetes mellitus (DM) is one of the most urgent problems of modern medicine inflicting colossal economic losses, early disability and mortality. Prevalence rate of diabetes is 1.5 to 6% of the population, and by 2035, experts of the International Diabetes Federation (IDF) expect an increase in the number of such patients of up to 600 million, with about 80% of these patients living in developing countries. Healing of wound defects in diabetes is characterized by a longer duration of the inflammation phase and a decrease in the activity of macrophages producing growth factors. There is a constant interest in the development of new methods for intra- and postoperative sanation of purulent foci in DFS. The immediate and long-term outcomes of treatment for 106 patients with purulent-necrotic complications of DFS without the phenomena of critical ischemia were analyzed. The patients were treated at the Orel Regional Clinical Hospital in the Orel city from 2008-2015. The main group of the study (the study group) included 55 patients. Their surgical treatment of the purulent foci was supplemented by ultrasonic cavitation using the Sonos 185 apparatus, Söring GmbH; the wound was drained by tubular drainage system withdrawn through counter openings. The wound was then oversewn, and after the operation, programmable sanation was applied using the original AMP-01 device. The control group consisted of 51 patients. After surgery on the purulent focus, the patients underwent standard local therapy - polyethylene glycol-based ointments, iodophor solutions; after resolution of the infection, we performed a foot plastic reconstruction, some patients wounds were healed by secondary tension. An analysis of the long-term outcomes of treatment for 35 patients with a neuroischemic form of the disease showed that the provided therapeutic and prophylactic measures in most cases allow maintaining a satisfactory blood supply to the feet and, thus, avoiding “high” limb amputation. Treatment activities included, as a rule, administration of lipostatic drugs and aspirin, quitting smoking, maintaining a sufficiently stable level of glycemia (not higher than 9 mmol/l). The long-term follow-up outcomes of the treatment were also better in the study group compared to the control group: there were significantly lower values for the number of late purulent complications (p = 0.0112), number of deaths (p = 0.0112) and number of cases of ischemia progression (p = 0.0095), while the number of cases of preserving the support ability of the foot was significantly higher (p = 0.0158). Programmable sanation technologies have a significant advantage over traditional techniques in the treatment of patients with purulent-necrotic complications of diabetic foot syndrome without critical ischemia. Their use reliably improves the quality of purulent focus sanation in diabetic foot syndrome, stimulates regenerative processes, which contributes to shortening the hospital stays and improving the immediate and long-term outcomes of the treatment.

Keywords: Diabetic Foot Syndrome, Sanation Technologies, Treatment, wound, purulent-necrotic complications.

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INTRODUCTION

Diabetes mellitus (DM) is one of the most urgent problems of modern medicine inflicting colossal economic losses, early disability and mortality. Prevalence rate of diabetes is 1.5 to 6% of the population [1,2], and by 2035, experts of the International Diabetes Federation (IDF) expect an increase in the number of such patients of up to 600 million, with about 80% of these patients living in developing countries [3]. One of the most severe complication of DM is diabetic foot syndrome (DFS), which causes painful suffering to the patient, and is a significant financial burden for the national health service of any country and world society as a whole [4-10]. Thus, the financial costs of the National Health Service in England and Wales for hospitalization and treatment of patients with complicated forms of DFS in 2010-2011 amounted to about 639-662 million pounds sterling [11]. The purulent complications of DFS account for 40-46% of all diabetic patients who have received inpatient treatment for a year, and the number of such patients increases further [12-14]. Trophic tissue changes and purulent necrotic lesions of the foot in DFS lead to “high” amputations in more than 85% cases [15]. Annually, up to 54,000 amputations of the lower extremities for the complications of DFS are made in the United States, and the mortality after such operations is up to 20 to 30% [16]. According to European researchers, mortality after «low» amputation within the first year was 24.6%, during the first 5 years - 66.3%; for «high» amputation, 1-year mortality rate was 43.3%, while the 5-year mortality rate was 83.3% [17]. Dealing with problems of DFS-related mortality and disability includes the adoption and following a strategy covering prevention and the implementation of an interdisciplinary approach to the treatment of trophic and purulent diabetic foot lesions [18-20]. The implementation of a set of such adequate and timely measures, according to the researchers, will help patients with diabetes to avoid amputation in almost 90% of cases [21]. The correct strategy for the local treatment of DFS is one of the key factors determining the final results of treatment. Issues of the general strategy of surgical treatment for purulent necrotic foci in DFS, as well as particular issues related to defining the scope and radicality of surgical treatment, continue to be studied and discussed [22-25]. No wonder international experts on DFS emphasize the precedence of surgical treatment of chronic wounds in diabetes before application of any local treatment [26-28]. Healing of wound defects in diabetes is characterized by a longer duration of the inflammation phase and a decrease in the activity of macrophages producing growth factors [29-32]. The role of matrix metalloprotease that significantly slows down the reparative processes in individuals with diabetes due to remodeling of the extracellular matrix and due to the prolonged collagen network formation has been proved [33,34]. Issues of assessing the availability of diabetic foot tissues to reconstructive operations remain urgent [19, 28, 35]. There is a constant interest in the development of new methods for intra- and postoperative sanation of purulent foci in DFS [36-39].

MATERIALS AND METHODS

The immediate and long-term outcomes of treatment for 106 patients with purulent-necrotic complications of DFS without the phenomena of critical ischemia were analyzed. The patients were treated at the Orel Regional Clinical Hospital in the Orel city from 2008-2015. Research work with a conclusion on the compliance of prearranged clinical studies with ethical norms and regulatory rules was approved by the ethical committee of the Federal State Budgetary Educational Institution of Higher Education “Voronezh State Medical University, N.N. Burdenko” of the Ministry of Health of the Russian Federation (Record No. 2 of March 29, 2012). The study was conducted in accordance with the requirements of the Declaration of Helsinki on the Good Clinical Practice (GCP) Guideline.

The main group of the study (the study group) included 55 patients. Their surgical treatment of the purulent foci was supplemented by ultrasonic cavitation using the Sonos 185 apparatus, Söring GmbH; the wound was drained by tubular drainage system withdrawn through counter openings. The wound was then oversewn, and after the operation, programmable sanation was applied using the original AMP-01 device (patent of invention No.2539165 of November 27, 2014). The control group consisted of 51 patients. After surgery on the purulent focus, the patients underwent standard local therapy - polyethylene glycol-based ointments, iodophor solutions; after resolution of the infection, we performed a foot plastic reconstruction, some patients wounds were healed by secondary tension.

The groups were composed of consecutive patients admitted to the hospital and meeting the inclusion criteria which was: patients with type-1 and type-2 diabetes mellitus; presence of purulent-necrotic complications of DFS without critical ischemia; transcutaneous oxygen tension (TcPO2) on the feet at least 30 mm Hg according to the transcutaneous oximetry measurements; II-IV grades of foot lesion according to the

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Wagner classification (1979); signed informed consent. Criteria for exclusion of patients: patients under 18 years of age; accompanying diseases in the stage of decompensation, circulatory and respiratory failure of the 3rd degree; endocrine-metabolic and hypothalamic obesity; the TcPO2 index in the foot skin below 30 mm Hg, I and V grades foot lesion according to the Wagner classification (1979).

The patients in the investigated groups were comparable in age, sex, DM type and clinical form of DFS (Table 1).

Table 1: Characteristics of patients of the study group and the control group

Characteristics		Study group (n=55)	Control group (n=51)	*p*
Average age (*M± σ*)		59±8	60±9	0.26*
Sex	males (abs..%)	25 (45.5 %)	23 (45.1 %)	1.00**
	females (abs..%)	30 (54.5 %)	28 (54.9 %)	
DM type	Type-1	5 (9.1 %)	4 (7.8 %)	1.00**
	Type-2	50 (90.9 %)	47 (92.2 %)	
Clinical form of DFS	neuropathic	32 (58.2 %)	31 (60.8 %)	0.66**
	neuroischemic	23 (41.8 %)	20 (39.2 %)	

Notes: * - according to Mann–Whitney U test ** - according to two-tailed Fisher's test

According to the lesion site of purulent-necrotic complications of DFS, all the patients in the investigated groups were divided by the lesion grades according to the Wagner classification (1979) (Table 2).

Table 2: Characteristics of patients in the investigated groups depending on the nosological form of purulent-necrotic complications of DFS and lesion extent in accordance with the Wagner classification (1979)

Nosological form of purulent-necrotic complications in the foot	Lesion extent in accordance with the Wagner classification (1979)	Study group (n=55)		Control group (n=51)		Total
		Abs.	%	Abs.	%	
Full-thickness ulcer	2	5*	9.1	4*	7.8	9
Full-thickness ulcer + Chronic toe osteomyelitis	3	3*	5.5	3*	5.9	6
Phlegmon toe + phlegmon foot	2	5*	9.1	6*	11.8	11
Toe osteomyelitis + phlegmon foot	3	8*	14.5	9*	17.6	17
Purulent wound after toe amputation or foot resection, previously performed in other medical institutions	3	14*	25.5	13*	25.5	27
Dry gangrene of one or more toes	4	12*	21.8	9*	17.6	21
Wet gangrene of a toe + phlegmon foot	4	8*	14.5	7*	13.7	15
Total:		55	100	51	100	106

Note: * - according to Pearson's chi-square test (for 50% of groups, expected frequencies are less than 5) there are no differences between the groups (*p*=0.989).

Combined therapy in both investigated groups included complete unloading of the foot, insulin therapy with fractional administration of adequate doses of the drug under the control of the glycemia level, etiotropic antibiotic therapy, metabolic and detoxification therapy, anticoagulants and immunomodulators were also prescribed.

In the neuropathic form of DFS, patients underwent radical surgical treatment. In the control group, the wound was not sutured, and after the inflammation had been stopped, plastic reconstruction of the foot was performed or the wound defect healed by secondary intention. In the study group, radical surgical debridement of suppurative foci and plastic reconstruction of the foot were performed within one stage, and in the postoperative period, the PAIS method was used.

In the neuroischemic form of DFS, surgical debridement of suppurative foci was performed in two variants, depending on the severity of the inflammatory process and the severity of the foot ischemia. In case of a foot phlegmon, wet gangrene of one or more toes, a purulent wound with blisters in the fascial spaces of the foot, a conditional-radical surgical treatment was performed during which a phlegmon was opened up with removal of necrotic tissues, gangrenous toes were amputated, and wounds were drained. The second stage of the surgical treatment included foot plastic reconstruction, when the wound was opened up, the foot skeleton was resected in the final version, the wound cavity was drained and, if necessary, the plastic wound closure was performed. When performing the foot plastic reconstruction, the aim was to make saving dissection of soft tissues over the bonesaw-line in such a way that their amount was sufficient to eliminate the resulting wound cavity and to suture without intention. In the study group of patients, the PAIS method was used in the postoperative period in all cases.

The second variant of surgical treatment of the purulent foci was implemented in patients of both investigated groups with a neuroischemic form of DFS in cases of dry gangrene of toes and granulating foot wounds after operations previously performed in other institutions. In the study group, surgical treatment of the purulent foci and foot plastic reconstruction were performed within one stage, and after the operation, the PAIS method was used. In the control group, interval surgical treatments of the purulent focus followed by the foot plastic reconstruction were performed, or the wound defect healed by the secondary intention. Primary surgical operations in patients in the investigated groups are presented in Table 3.

Table 3: Primary operations in the patients of the investigated groups

Primary operations	Study group (n=55)		Control group (n=51)		Total
	Abs.	%	Abs.	%	
Surgical treatment	9*	16.4	9*	17.6	18
Phlegmon opening up	13*	23.6	18*	35.3	31
Amputation of a toe	9*	16.4	6*	11.8	15
Amputation of the distal portion of the foot	12*	21.8	8*	15.7	20
Transmetatarsal amputation of the foot	12*	21.8	10*	19.6	22
Total:	55	100	51	100	106

Note: * - according to Pearson's chi-square test (expected frequencies are less than 5) there are no differences between the groups (p=0.72).

The PAIS method was implemented as follows. After the surgical treatment of the purulent foci, drains were located in the lowest places of the cavity of the purulent focus and withdrawn through the counter-lines. The wound over the drains was sutured, and the drainage system was connected to the original device AMP-01. With the help of the device, the sanation program was simulated with the adjustment of the parameters of cyclic injection of the antiseptic into the purulent cavity and the parameters of aspiration of the spent solution (speed, time, volume of injection or aspiration). Programmable sanation was carried out every 3 hours, being alternated with a vacuuming period in the purulent cavity (1 hour) created by the device AMP-01 in the aspiration mode. At the same time, the level of vacuum in the cavity of the purulent focus was maintained at a level of 60-80 mm Hg and regulated by a pressure gauge. This method was used after the operation during 5 to 8 days, then active aspiration was performed.

In order to evaluate the macrodynamics of the lower limbs, the ultrasound duplex scanning of the arteries was carried out by the Acuson-128 XP / 10 system (USA) using a standard technique with a linear sensor with a frequency of 7-15 MHz. Transcutaneous oximetry was performed by means of a TCM 400 device, Radiometer Medical ApS (Denmark).

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All the patients of the investigated groups underwent general clinical laboratory test, bacteriological examination of the wound fluid with the antibiotic sensitivity test. The seedings from purulent foci were carried out on the day of admission, as well as on days 3, 5, 7, 9, 12 from the start of treatment. To quantify the bacterial contents of the wounds of the foot, the colony-forming units (CFU/g) were used. The immediate outcomes of the treatment for the patients with purulent-necrotic complications of DFS were assessed by the duration of inpatient treatment, the postoperative mortality rate, the number of purulent complications and "high" amputations performed, the estimation of the cases of preserving the supporting function of the foot. The long-term outcomes of the treatment for the patients with purulent-necrotic complications of DFS were analyzed for the period at least 2 years after the initial course of combined treatment by evaluating long-term clinical and functional outcomes and using a questionnaire. At the same time, the long-term outcomes were evaluated according to the following criteria: the number of "high" amputations performed at different observation periods; the state of blood flow in the arteries of the preserved limb; the number of late purulent complications in the form of the phlegmon foot or surgical scar fistula; the assessment of the support ability of the preserved foot.

The work was performed in the design of a simple randomized comparative controlled study in parallel groups. Randomization was performed by random sampling technique. Due to nonparametric distribution of values investigated, the contingency tables were made, the mean, standard deviation, median, mode, interquartile range (25th and 75th quartile), chance, absolute and relative risks were calculated. Confidence intervals were defined for quantitative traits and relative risks of binary traits. The reliability of the differences in the data obtained was evaluated using the Mann-Whitney test for unrelated groups and the Wilcoxon test for related groups. To compare independent qualitative characteristics (age, sex, stage, etc.), Pearson's chi-square-criterion was used. The reliability of the differences between unrelated groups was estimated using the Fisher's exact test (*p*-criterion), since one of the expected frequencies was no more than 5. The null statistical hypothesis was rejected at <0.05.

RESULTS AND DISCUSSION

On patients' admission to the hospital, the median value of microbial contents of the wounds was 50×10^{10} CFU/ml of the wound fluid (interquartile range from 40×10^{10} to 65×10^{10} CFU/ml of the wound fluid) for the study group, and 50×10^{10} CFU/ml of the wound fluid (interquartile range from 40×10^{10} to 60×10^{10} CFU/ml of the wound fluid, $p = 0.57$) for the control group. Five days after the surgical treatment of the purulent foci, the median value of the microbial contents of the wounds was 6×10^{3} CFU/ml of the wound fluid (interquartile range from 5×10^{3} to 7.5×10^{3} CFU/ml of the wound fluid) in the patients of the study group. In the control group, for the same date, the median value of the microbial contents of the wounds was 5×10^{5} CFU/ml of the wound fluid (interquartile range from 3×10^{5} to 6×10^{5} CFU/ml of the wound fluid, p <0.001). The value of microbial contents of wounds in patients of the study group decreased below the critical level on average on Days 3-4, in the control group - on average on Days 6-7 after the operation (Figure 1).

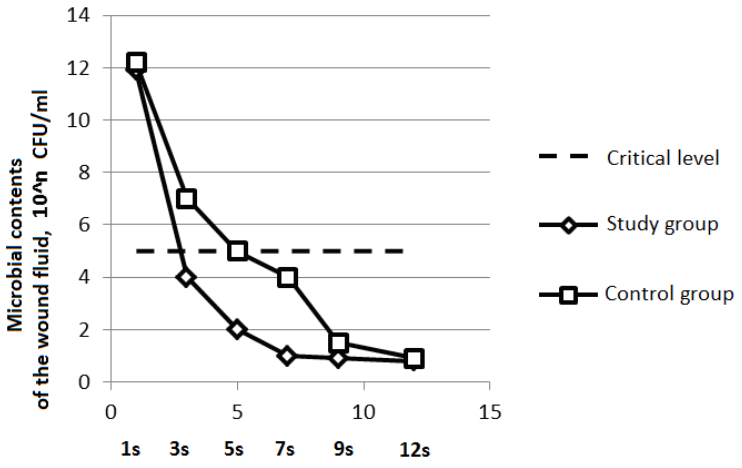

Fig 1: Dynamics of the level of microbial contents of the wound fluid in patients with purulent-necrotic complications of DFS in the groups compared

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In the study group, in-hospital stay for patients with purulent-necrotic complications of DFS (median value and interquartile range) was 21 bed-days (21 to 23 bed-days), in the control group - 29 bed days (27 to 30 hospital days, p <0.001). The immediate outcomes of treatment were analyzed in 106 operated patients (Table 4).

Table 4: Immediate outcomes of the treatment for patients with purulent-necrotic complications of DFS in the groups investigated

		Outcome	No outcome	ER	RR	II RR	OR	II OR	*F*
Postoperative mortality	Study group	3	52	0.055	0.556	0.140	0.531	0.098	0.477
	Control group	5	46	0.098		2.211		3.899	
Purulent complications	Study group	5	50	0.091	0.357	0.137	0.292	0.064	0.037
	Control group	13	38	0.255		0.930		0.744	
Amputation	Study group	4	51	0.073	0.285	0.099	0.229	0.072	0.016
	Control group	13	38	0.255		0.819		0.842	
Supporting function of the foot is preserved in patients discharged	Study group	45	7	0.865	1.327	1.047	3.429	1.260	0.017
	Control group	30	16	0.652		1.681		9.331	

Notes: ER – absolute risk, RR – relative risk, II RR – 95% confidence interval for relative risk, OR – odd ratio, II OR – 95% confidence interval for odd ratio, *F* – two-tailed Fisher's test value

Postoperative mortality in the study group of patients was 5.5%, in the control group - 9.8%. All fatal outcomes are noted after «high» amputations. At the significance level p = 0,477, the hypothesis about no differences between the groups in terms of the number of lethal cases was accepted. A possible explanation for this fact is a small sample of patients in this study and a low level of mortality in the investigated groups. The cause of death for three patients was extensive myocardial infarction, for two patients - acute renal failure. One patient died of a stroke, and two others - from severe sepsis resulted from wet gangrene of the foot affecting the shin after the thigh amputation.

Purulent complications were observed in the study group of patients in 5 cases (9.1%), and in the control group - in 13 cases (25.5%, p = 0.037). The supporting function of the foot was preserved in the study group in 45 patients discharged (86.5%), in the control group - in 30 cases (65.2%, p = 0.017). Due to the lack of the effect, «high» amputations were performed in the study group in 4 cases (7.3%): in two cases at the level of the upper third of the shin, and in the other two cases at the thigh level. In the control group, amputation was performed in 13 cases (25.5%, p = 0.016): 5 cases of the shin amputation, and 8 cases of the above-knee amputations.

The long-term outcomes of the treatment were studied in 86 (81.1%) of 106 patients with purulent-necrotic complications of DFS within 2 to 7 years after the combined treatment by evaluating long-term clinical and functional results and using a questionnaire. 45 of 55 patients in the study group (81.8%) and 41 of 51 patients in the control group (80.2%) were questioned and examined. Patients of the investigated groups were comparable by the clinical form of DFS (Table 5).

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Table 5: Distribution of the patients in the investigated groups according to the clinical form of DFS for estimation of the long-term outcomes

Clinical form of DFS	Study group (of 55)	Control group (of 51)	Total	Fisher's criterion, *p*
neuropathic form	26	25	51	1.0000
neuroischemic form	19	16	35	1.0000
Total:	45	41	86	1.0000

Notes: no significant differences between groups were found (p>0,05)

Of 86 patients examined, 51 were called into the hospital, 17 came to the consultation on their own initiative, 3 gave comprehensive answers to our questionnaire at a distance, and for 15 patients information was received from medical institutions and other sources at their places of residence.

According to the results of questioning and examination of 86 patients, 32 of them (37.2%) had different late complications related to the previously operated limb. Long-term outcomes of treatment for patients with purulent-necrotic complications of DFS of both investigated groups are summarized in Table 6.

Table 6: Long-term outcomes of treatment for the patients with purulent-necrotic complications of DFS of both investigated groups

Treatment outcomes	Study group (n=45)		Control group (n=41)		Total (n=86)		Fisher's criterion, *p*
	abs	%	abs	%	abs	%	
Late purulent complications in the form of phlegmon foot or postoperative scar fistula	2*	4.4	10*	24.4	12	13.95	0.0112
Support ability of the foot	32*	71.1	18*	43.9	50	58.1	0.0158
Progression of foot ischemia	5*	11.1	15*	36.6	20	23.3	0.0095
"High" amputation of the limb due to the ischemia progression	2	4.4	5	12.2	7	8.1	0.2505
Number of deaths, including recurrence of purulent-necrotic complications of DFS resulting in sepsis	2* 1	4.4 2.2	10* 4	24.4 9.8	12 5	13.95 5.8	0.0112 0.1875

Note:* – significant differences (p<0.05) between the study group and the control group are presented

During the long-term follow-up examination, a significant increase in the number of deaths in the control group compared to the study group was noted (p = 0.0112). The causes of such late deaths were acute cerebrovascular accident - 2 cases, myocardial infarction - 2 cases, lung cancer - 1 case, progressive renal failure - 1 case. Recurrence of the purulent-necrotic complications of DFS resulting in sepsis caused 6 deaths – 1 patient in the study group and 5 patients in the control group (p = 0.1875).

Number of late complications in the form of progression of foot ischemia was significantly lower in the study group compared to the control group (p = 0.0095). In 7 patients, foot ischemia became irreversible, which led to the need for a "high" amputation of the limb: 3 cases of thigh amputation and 4 cases of shin amputation. There was an increase in the number of amputations in the control group compared to the study group, but this increase proved to be unreliable (p = 0.2505).

An analysis of the long-term outcomes of treatment for 35 patients with a neuroischemic form of the disease showed that the provided therapeutic and prophylactic measures in most cases allow maintaining a satisfactory blood supply to the feet and, thus, avoiding "high" limb amputation. Treatment activities included, as a rule, administration of lipostatic drugs and aspirin, quitting smoking, maintaining a sufficiently stable level of glycemia (not higher than 9 mmol/l).

The development of late purulent complications in the form of a phlegmon foot or a postoperative scar fistula in the long-term period was significantly lower in the study group than in the control group (p = 0.0112).

The long-term follow-up examination showed a significant increase in the number of cases of preservation of support ability of the foot in the study group compared to the control group (p = 0.0158).

The wounds in DFS are known to be characterized by a more prolonged course of the inflammation phase, a decrease in the activity of cells involved in the inflammation process, primarily macrophages producing growth factors [28-31]. Thus proving the role of matrix metalloprotease, which significantly inhibits the regeneration processes in diabetes due to the slowing down the production of the extracellular matrix and due to the prolonged organization of the collagen network [32-35]. To date, various methods of intra- and postoperative sanation of purulent foci in DFS have been proposed. The study conducted proved the efficiency of the combined approach to the treatment of patients with purulent-necrotic complications of DFS without critical ischemia compared to the traditional methods. The use of ultrasound for surgical treatment of purulent foci, early closure of the wound, the use of programmable sanations in combination with vacuum technologies in the postoperative period have made it possible to improve the outcomes of treatment for the patients of this nosology. During the study, faster purification of purulent foci from microbial bodies in DFS was reliably proven (p <0.001), and the duration of inpatient treatment for the patients with purulent-necrotic complications of DFS of the study group decreased 1.3 times. When assessing the immediate results in the study group, there was a significant decrease in the number of purulent complications (p = 0.037), a decreased number of “high” amputations (p = 0.016), and an increased probability of preserving the support function of the foot in the study (p = 0.017).

The long-term follow-up outcomes of the treatment were also better in the study group compared to the control group: there were significantly lower values for the number of late purulent complications (p = 0.0112), number of deaths (p = 0.0112) and number of cases of ischemia progression (p = 0.0095), while the number of cases of preserving the support ability of the foot was significantly higher (p = 0.0158).

CONCLUSION

Programmable sanation technologies have a significant advantage over traditional techniques in the treatment of patients with purulent-necrotic complications of diabetic foot syndrome without critical ischemia. Their use reliably improves the quality of purulent focus sanation in diabetic foot syndrome, stimulates regenerative processes, which contributes to shortening the hospital stays and improving the immediate and long-term outcomes of the treatment.

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