To Some Questions About the Treatment of Diabetic Foot Syndrome in Patients with Covid-19

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ABSTRACT

Background. Wound healing in diabetic foot syndrome is one of the serious problems in the treatment of patients with diabetes mellitus. Purulent-necrotic diseases of the foot are the most common cause of disability and death in patients with diabetes mellitus. Amputation of the lower limb is most often caused by the occurrence of ischemic gangrene, neuropathic ulcers, and the progressive development of necrosis and infection. This is due to the atypical course of the wound process in diabetes mellitus.

Material. The results of plastic surgery to eliminate wounds in patients with diabetic foot syndrome are analyzed. Morphological, cytological and planimetric research methods were used to evaluate the results.

Conclusion. Features of the course of the wound process after dermaplasty in patients with diabetic foot syndrome are the wave-like course of inflammatory processes with a subsequent decrease in their intensity. The use of Azacytidine changes the course of the process of engraftment of the skin flap in diabetic foot syndrome, reducing the duration and intensity of inflammation.

Keywords: diabetic foot syndrome, purulent-necrotic diseases of soft tissues, dermaplasty, Azacytidine.

Introduction

The frequency of high amputations of the lower extremities for diabetic foot syndrome is 6-8 per 1000 patients. At the same time, postoperative mortality with amputations "above the knee" reaches 40-68% during the first 5 years. [1]

The economic costs of treating diabetic ulcers are high. In this regard, it is necessary to develop effective and cost-effective treatment strategies to improve the outcomes of operations in this contingent of patients. [2]

Currently, local operations are increasingly used for purulent-necrotic processes in patients with diabetic foot syndrome. A significant part of such interventions leads to the formation of extensive granulating wound surfaces, which, with prolonged self-healing by "secondary tension", inevitably turn into ulcers. In plastic surgery, there are several methods for closing wounds on the foot in patients without diabetes, but indications for plastic surgery on the distal parts of the lower extremities in patients with diabetes mellitus are very limited. [3]

It is known that the presence of diabetic foot syndrome often leads to skin necrosis and the development of purulent complications in the postoperative period. Metabolic, immune, and hemorheological disorders characteristic of diabetic foot syndrome provokes the progression of the purulent-necrotic process and are the cause of unsatisfactory treatment results. Therefore, plastic surgery on a diabetic foot is rarely performed. All this determines the need for an in-depth study of the clinical and

morphological processes of engraftment of the dermatome flap in patients with diabetic foot syndrome and improvement of the technique of plastic closure of wounds on the foot. [4,5,6]

Material And Methods

This study is based on the observation of 61 patients with diabetic foot syndrome, who from 2020 to 2022 years of age in the department of surgical infection of the multidisciplinary clinic of the Tashkent Medical Academy underwent local operations for purulent-necrotic lesions.

In all patients, it was not possible to complete the operation by suturing the wound tightly due to the extensiveness of the skin defect formed after necrectomy, and the pronounced tension of the wound edges when trying to bring them closer together, so the final stage of treatment was the delayed free dermatomic plasty of the granulating wound with a split skin flap.

All patients were randomized into 2 groups. The first group (control) included 25 patients in whom dermatomic plasty was performed according to the traditional method. In the second group (main), which included 36 patients, dermaplasty was performed against the background of preliminary use of Azacytidine.

We did not reveal significant differences between the control and main groups on the following grounds age, sex, type, severity, and degree of compensation for diabetes mellitus, concomitant diseases, forms of diabetic foot syndrome, and drug therapy.

In preparation for the plastic closure of the wound and the postoperative period, patients of both groups used the same type of drug treatment. The standard scheme included glycemic compensation, antibiotic therapy, pathogenetic therapy depending on the form of diabetic foot syndrome, complete unloading of the affected limb, staged necrectomy, and local wound treatment.

To remove the dermatome flap, a disc dermatome was used. A perforated skin flap with a thickness of 0.3-0.5 mm was used for plastic surgery of wounds on the back of the foot and 0.5-0.8 mm for wounds on the sole.

In the main group, all patients were intraoperatively administered antimetabolite Azacytidine. The drug was administered intravenously, in a stream, at a dose of 5 mg per 1 kg of body weight once

In the postoperative period, in both groups, the area of engraftment of the graft was estimated by planimetry. The area of the viable skin flap was measured by transferring its contours to a polyethene film and then determining the area of the site using millimetre paper.

We considered the result of the operation to be positive if the accustomed area was more than 50% of the graft area.

The biopsy specimens were taken sharply in the site of a macroscopically viable transplanted skin flap for the entire thickness of the skin along with the perceiving bed. The size of the biopsy is 3x3 mm. Drugs taken from patients of both groups were studied on the 4th, 6th, 8th, and 12th day after plastic surgery. The material was fixed in a 10% solution of neutral formalin and poured with paraffin. According to the adopted technique. The paraffined sections were stained with hematoxylin and eosin, and by special methods of staining according to van Gizon. In the resulting sections, the number of cellular elements (neutrophils, macrophages, lymphocytes, fibroblasts, plasmacytes) was calculated using the "point counting" method, and the number of morphological elements in 10 visual fields, each of 25 points, was calculated. The relative bulk density of collagen, elastic and reticular fibres was calculated.

In the transplanted flap, semi-quantitatively, according to the 3-point system, the severity of signs of destruction and repair of dystrophic changes in the nuclei of the epithelium, paranecrotic and necrobiotic processes in the epidermis, subdermal blisters and intraepidermal blisters, necrotic areas in the dermis of the flap, necrotic areas of the perceiving bed, vasodilation, sclerosis and hyalinosis of their walls, stasis, blood clots in the lumen of the vessel, oedema of the dermis, germination of blood vessels in the dermis of the flap, the cords of the epidermis (acanthosis) in the dermis of the flap Thus, we emphasized the clarifying role of the morphometric method, which allows achieving greater objectification of scientific research.

Statistical processing of the obtained numerical data was carried out using the recommended statistical methods and the statistical package STATISTIKA 50. The numerical characteristics of the variation series were determined - M, m, t, 8. To calculate the statistical significance of the differences (p) between the two data series, the Student's criterion was used. To assess the statistical reliability of the change in the indicator during treatment, Friedman's criterion was used the above criteria are applied to samples with a normal distribution.

Results

Engraftment of the dermatome flap against the background of diabetes mellitus is characterized by the resumption of oedema and infiltration of foot tissues. On the 6th day after the plastic surgery, epidermal blisters with cloudy contents were observed in those areas of the grafts that subsequently underwent rejection and necrosis. After the removal of the exfoliated epidermis, the phenomena of focal changes in the colour of the dermis were visible, and purple-bluish spots appeared. Granulations of the bed in these areas were swollen, and dull, there was pus. By the 9th day of the postoperative period in such places, the colour of the transplanted flap changed over a larger area and its partial detachment occurred. Complete detachment of the graft or its part from the perceiving bed and necrosis of the flap or part of it we observed 12 or 14 days after transplantation.

In the morphological study of biopsy specimens, it was by the 12th and 14th days that an increase in the manifestations of destruction in the flap expressed on a 3-point scale (destruction of the epidermis $p<0.05$, necrotic areas of the epidermis $p<0.01$, necrosis of the dermis $p<0.05$) was noted. In addition, a significant expansion and thrombosis of blood vessels, and stasis of shaped elements ($p<0.05$) in the same time frame were revealed.

Administration of Azacytidine led to a decrease in the clinical signs of an inflammatory response in the receptor bed. Morphologically, this was accompanied by a lower severity of destructive processes in the epidermis and dermis without increasing them by the late stages (14 days). The phenomena of paranecrosis and necrobiosis of the epithelium manifested themselves to a much greater extent in the comparison group, reliable differences were detected 14 days after autograft transplantation.

The processes of formation of necrosis of the actual dermis of the transplanted flap, as well as paranecrotic and necrobiotic processes in the epidermis in patients with diabetes mellitus who did not receive the drug, proceeded in waves, with the development of pronounced destruction on the 6th day, a decrease in its signs to 12 days and a repeated increase to 14 days. In the group of patients receiving Azacytidine, the number of patch areas that underwent destruction from 6- The differences between the 12- and 14-day groups were statistically significant.

Microvasculatory disorders (vasodilation, stasis of the sensing bed) were also significantly more pronounced in the late timing of engraftment of the flap (at 12 and 14 days) in patients who did not receive Azacytidine. No significant differences were found between the groups in the assessment of bed oedema and dystrophic changes in the epithelial nuclei.

As a manifestation of reparative processes, there was a significant increase in the number of areas of the newly formed epidermis in the transplanted flap on the 6th and 9th day after the operation by more than 2 times in the group of patients receiving Azacytidine. By the 12th and 14th days, the beginning of epithelial growth is noted and in the flaps of patients of the comparison group and the specified differences between the groups decrease.

In the study of neutrophil granulocytes in the sensing bed and dermis of the flap, a tendency to an earlier decrease in neutrophilic infiltration in the process of engraftment of the autodermal flap differences do not reach a statistically significant level, but there is a tendency to reduce the content of neutrophil granulocytes on the 9-day after autodermaplasty to 0.72±0.36 cells / mm2 in the group of patients receiving Azacytidine compared with 1.54±0.62 cl etc. / mm^2 in the group of patients who did not receive the drug.

Lymphocytic infiltration in patients entrusted with Azacytidine was extremely mild and increased slightly during the engraftment of the flap (0.2±0.14 cell/mm^2 on the 6-day after transplantation to 1.2±0.47 cell/mm^2 to 14 days the postoperative period). In the group of patients who did not receive the drug, the indicators of lymphocytic infiltration were much higher than those in comparison with the main group of patients, increasing from 0.93±0.32 cell/mm^2 per 6-day to I4.6±2.6 cell/mm^2 on 14- day, respectively

When comparing the number of plasmacytes in the preparations, a significant decrease in the presence of these cells in the biopsy specimens of the flap of patients with diabetic foot syndrome treated with Azacytidine was detected. In the dynamics from the sixth to the twelfth day of the postoperative period, the indicators of plasma filtration by plasma cells of the flap bed increased in both groups from 0.56±0.23 cell/mm^2 to 5.6±2.2 cell/mm^2 in the study group and from 3.41±0.81 cell/mm^2 to 21.0±3.2 cell/mm^2 in the comparison group and these differences persisted further to 14 days. These differences are statistically significant

Differences in the dynamics of the proliferative activity of fibroblasts led to the fact that the content of these cells in the preparations of patients receiving Azacytidine is significantly lower by 9 (6.68±1.26 cell/mm^2 and 12.20±2.49 cell/mm^2) and 14-day (6.76±1.14 cell/mm^2 and 11.45±2.64 cell/mm^2) after surgery compared with similar patients who did not receive the drug.

The drug also leads to a slowdown in the synthesis and accumulation of collagen, because of which in the biopsy specimens of patients receiving Azacytidine, the volume density of collagen fibres on the 12th and 14th day after surgery is significantly lower than in patients of the comparison group (2.2±0.40 and 5.0±0.35 on the 12th day and 2.3±0.31 and 6.14±0.36 on the 14th day, respectively).

The drug does not have a significant effect on the increase in the volume density of elastic fibres throughout the process of engraftment of the skin flap and reticular fibres.

When analyzing the outcomes of plastic closure of the wound, it was found that necrosis of more than 50% of the area occurred in a significant number of patients in the control group who did not receive Azacytidine (11 out of 25 patients). With the use of antimetabolite in the main group of patients during autodermaplasty, rejection and necrosis of the graft occurred much less often (8.3% ±4.6% versus 44% ±9.9% in the control group), the differences are statistically significant.

Discussion

The problem of the final closure of the wound in the surgical treatment of purulent-necrotic processes on the foot in diabetes mellitus is still far from a final solution. Of the entire spectrum of plastic surgery, dermatome skin plasty has established itself as a simple, safe, and affordable procedure, but the chances of successful engraftment of a split skin flap in diabetic foot syndrome without appropriate wound preparation and medical support leave much to be desired. In this clinical study, we conducted a study of the effectiveness of Azacytidine, which aims to reduce the inflammatory response in the bed in response to flap transplantation and protect the graft. [11,12]

After plastic surgery, an inflammatory reaction is activated in the sensing bed in response to flap transplantation. As a result of the dysfunction of the cells of the key cells of inflammation caused by hyperglycemia, there is no complete resolution of infiltration, on the contrary - the wound acquires the status of chronic inflammation, which is characterized by the presence in the tissues of a significant number of lymphocytes and plasmacytes. As can be seen from the study of the morphological picture of the biopsy specimens of the perceiving bed and flap in patients with diabetes mellitus, the change of polymorphonuclear infiltration to lymphocytic infiltration is slowed down, at the terms of 12-14 days. There is a pronounced lymphocytic infiltration involving a significant number of plasma cells. All this prevents the engraftment of the flap and leads to its lysis both immediately after transplantation and later. in patients with diabetes mellitus, signs of destruction (dystrophic changes in the nuclei, necrotic areas

in the flap dermis and epidermis) have some tendency to increase in the late stages (14 days) after plastic closure of the wound. [7,8]

A single administration of a small dose of Azacytidine directly at the time of transplantation contributes to faster and more complete completion of the phase of inflammation in the wound, which is manifested by a twofold decrease in the number of lymphocytes in the wound and a fourfold decrease in plasma cells. There is a tendency to accelerate the resorption of infiltration of bed tissues by neutrophilic granulocytes. Relief of the inflammatory reaction in patients receiving Azacytidine is accompanied by a lower severity of signs of the destruction of the epidermis and dermis without an increase in necrotic processes by late dates, as well as an earlier appearance of epidermal cords in the dermis flap. [9,10]

We also found a slight decrease in the proliferative activity of fibroblasts under the influence of Azacytidine. A with a selective slowdown in the synthesis and accumulation of collagen. At the same time, the drug did not affect the rate of formation of reticular and elastic fibres. This feature of the effect of Azacytidine is well-known and described in many works. [11,12] It should be noted that clinically in all cases the strength of the formed fibrous layer was quite sufficient in our patients, even with the localization of the accustomed flap on the plantar surface carrying a significant load. [13-15]

Thus, the results obtained indicate a positive effect of Azacytidine on the transplanted dermatomic skin flap, manifested in a decrease in the prevalence and intensity of the exudative phase of the inflammatory reaction, as well as a decrease in the risk of necrosis and rejection of the skin graft in patients with diabetic foot syndrome.

Conclusion

The clinical and morphological features of engraftment of an autograft in diabetic foot syndrome consist of a wave-like course of destructive processes with a decrease in their intensity for 12 days after plastic surgery and a repeated increase later. The use of Azacytidine changes the course of the process of engraftment of the skin flap in diabetic foot syndrome, reducing the duration and intensity of inflammation, which is manifested by a twofold decrease in the level of lymphocytes and a fourfold decrease in the level of plasma cells in the transplanted flap. Preparation of the wound surface in diabetic foot syndrome for plastic closure, including a single injection of Azacytidine according to the proposed technique, it was possible to reduce the number of patients with 50% necrosis of the transplanted flap by 5.3 times (from 44.0±9.9% to 8.3±4.6%).

Ethics approval and consent to participate - All patients gave written informed consent to participate in the study.

Consent for publication - The study is valid, and recognition by the organization is not required. The author agrees to open the publication

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