UDC 616.379 – 008.64:617.586:546.17

CLINICAL AND LABORATORY EVALUATION OF APPLICATION OF AIR-PLASMA FLOWS OF NITROGEN MONOXIDE - IN THE TREATMENT OF NECROTIZING ULCERATIVE COMPLICATIONS OF THE DIABETIC FOOT SYNDROME

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In the recent years, the air-plasma flow of nitric oxide is being used for treatment of purulent wounds. Discovery of endogenous nitric oxide was the biggest event in biology and medicine of the second half of the 20th century. By determining clinical and laboratory parameters, the effect of exogenous nitrogen monoxide on the dynamics of the inflammatory process was studied in patients with the diabetic foot syndrome having necrotizing ulcerative lesions. The basis of the work lies in the analysis of the comprehensive treatment of 224 patients that were divided into two groups. The main group included 104 patients that were being treated using the traditional combined therapy coupled with application of exogenous nitric oxide. Topically, the therapy consisting of the air-plasma flow of nitrogen monoxide was applied on the wound surface in the therapeutic mode along with using a manipulator with a 2-mm diameter of the outlet, 2 мм, с exposure of 30 sec. per 1 cm^2 from the distance of 5 cm, up to 15 sessions daily. The control arm included 120 patients who were receiving traditional treatment.

Key words: necrotizing ulcerative lesions, экзогенный монооксид азота, синдром диабетической стопы

CLINICAL-LABORATORY EVALUATION OF APPLICATION OF AIR-PLASMA FLOWS OF NITROGEN MONOXIDE IN THE TREATMENT OF NECROTIZING SINDROMA DIABETIC FOOT COMPLICATIONS

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In recent years, for the treatment of purulent wounds using air-plasma flow of nitric oxide. Discovery of endogenous nitric oxide was the biggest event of Biology and Medicine of the second half of the twentieth century. By determining the clinical and laboratory parameters examined the effect of exogenous nitrogen monoxide on the dynamics of the inflammatory process in patients with ulcer-necrotic lesions in diabetic foot. The basis of the analysis of the results is a comprehensive treatment of 224 patients, all patients were divided into two groups. Study group included 104 patients who were treated with conventional combined therapy in combination with exogenous nitrogen monoxide. Topically to the wound surface treatment was carried out air-plasma flow of nitrogen monoxide in the therapeutic mode using a manipulator with a diameter of 2 mm outlet, with an exposure of 30 seconds per 1 cm^2 at a distance of 5 cm to 15 daily sessions. The control group included 120 patients who received standard treatment.

Keywords: ulcer-necrotic lesions, exogenous nitrogen monoxide, diabetic foot syndrome

The diabetic foot syndrome presents a set of malfunctions of the lower extremity with a high probability of the development of necrotizing ulcerative processes, and is encountered in 50–80 % of patients with diabetes mellitus [7].

Using the newest medical technologies in surgery allows achieving better results of treating patients with inflammatory processes. Successes reached in the development of highly effective electric-arc plasma generators, as well as prospectivity of application of certain physical methods of action upon biological tissues, have led to the emergence of a new trend in medicine – plasma surgery. broad usage of the new method has been restrained by the lack of standard industrial samples of plasma tools [6].

Over the last years, air-plasma flow of nitric oxide (NO therapy) is being used to treat purulent wounds. Discovery of endogenous nitric oxide (NO), which is produced by way of NO-synthesis and performs the functions of a universal regulator/meddenger, has been the biggest event in biology and medicine of the second half of the 20th century [10].

Nitrogen monoxide is a short-lived in vivo gaseous inorganic compound. The NO molecule appears to be a highly reactive free radical (NO) capable to transform into the ionized forms. It is generally acknowledged that nitric oxide, may perform not only the functions of a secondary messenger but also those of an neurotransmitter, autocrin and paracrin regulator, and in some cases those of a hormone-like inductor [6].

Nitrogen monoxide suppresses the growth of micro-organisms, which is particularly important in the presence of antibiotic-resistant microbial flora, improves the vascular tropism and the blood supply of tissues, which positively affects the reparative processes and increases the concentration of antibacterial preparations in the focus of lesion [9].

Nitric oxide takes part in the regulation of the blood vessels tone, playing the role of the vaso-relaxing factor. It suppresses the aggregation of thrombocytes and their adhesion on the walls of the vessels. The importance of Nitrogen monoxide in the improvement of local immunity is related to the stimulation of macrophages, induction of cytokines, T-lymphocytes and a number of immunoglobulins [2].

Obtaining exogenous nitrogen monoxide became possible with the assistance of the Plazon apparatus developed and manufactured at the N.E.Bauman Moscow State Technical University under the guidance of Academician A.V. Pekshev at the laboratory of N.P. Kozlov (RF Government Prize for theyear 2003) [8, 10].

The purpose of the study: by determining the clinical and laboratory parameters, study the impact of exogenous nitrogen monoxide on the course of the inflammatory process in patients with necrotizing ulcerous lesions under the diabetic foot syndrome.

Materials and methods of the study

The basis of the study lies in the analysis of the results of comprehensive treatment of 224 patients with necrotizing ulcerous complications of the diabetic foot syndrome. All patients were divided into two arms. The main group included 104 patients that were being treated using the traditional combined therapy coupled with application of NO therapy. Topically, the therapy consisting of the air-plasma flow of nitrogen monoxide was applied on the wound surface in the therapeutic mode along with using a manipulator with a 2-mm diameter of the outlet, which allowed obtaining low-temperature (25–40°C) gas flows with a high content of the NO molecules (up to 2,000–3,000 ppm), with exposure of 30 sec. per 1 cm^2 from the distance of 5 cm in up to 15 sessions daily. In cases of presence of necrotically modified tissues, they were removed in the coagulation mode.

In the control group, 120 patients were included, who were receiving traditional treatment. Included in the study were only the patients with the diabetic foot syndrome, having lesions of 1–4 degree under Wagner F.W. classification.

Most of the patients were in the age of the highest ability to work – from 30 to 60 years (54 in the main group (51.9 %), 63 in the control group (52.6 %)). At the same time, a significant part consisted of elderly and old patients (50 in the main group (48.1 %), in the control group – 57 (47.4 %)), which is characteristic for patients with necrotizing ulcerous lesions under the diabetic foot syndrome. There were 116 females (51.8 %), and 108 males (48.2 %). Analysis of anamnestic data has shown that 29 patients (12.8 %) had the duration of illness up to 5 years, 78 patients (34.9 %) – up to 10 years, and 117 patients (52.3 %) – above 10 years. No statistically significant differences between the two groups as to the gender, age, and type of pathology were revealed.

The dynamic pattern of changes in the wound process was being monitored by measuring the body temperature, evaluating the pronouncement of the pain syndrome, edema of the surrounding tissues, amount of the wound fluid, as well as the terms of appearance of the granulation tissue and measuring the area of the wound surface.

The dynamic pattern of the pain syndrome was studied by questioning of the patients on feeling pain, using the visual analog scale (VAS) [4].

The dynamic pattern of the change in the wounds area was evaluated using the index of L.N. Popova [5] and the index of V.S. Peschansky [3], which were determined on the 5th, 10th and 15th days of the patient's stay in the inpatient facility.

Laboratory control was performed by calculating the amount of white blood cells, determining the intensity of the differential leukocyte count by the leukocyte index of intoxication (LII) on the 1st, 5th,, 10th and 15th days of the patient's stay in the inpatient facility.

Statistical processing was performed using the package of statistical computer programs "Biostat" (1998) and Microsoft Office® Excel® (2007). In the study, the contingency tables analysis was used, where the Chi square value was determined. In all statistical analysis studies, the critical value of the p-level was assumed to be equal to 0.05.

Results of the study and their discussion

When body temperature was measured at the time of admission, the 79 patients (65.83 %) in the control group had hyperthermia, while 61 patients (58.65 %) in the main group had a higher temperature ($p = 0.333$). Normalization of the body temperature (assuming ≤ 37.0°C as the norm) occurred by the $6.72 \pm 1{,}54$ day in the control group of patients, and by the 5.16 ± 1.2 days in the main group ($p = 0.646$).

The pain syndrome was arrested by the 4.39 ± 0.6 days on the average in the control group of patients, and by the 2.88 ± 0.53 days on the average in the main group of patients ($p = 0.002$).

The dynamic pattern of edema of the surrounding tissues was evaluated by daily examination of wounds at dressings. Edema of the surrounding tissues was arrested in the control group by the 6.79 ± 0.97 days on the average, and in the main group by the 4.25 ± 0.54 days on the average ($p < 0.001$).

The amount of wound fluid was evaluated visually depending on the dressing impregnation by the wound fluid. Decrease in the amount of wound fluid in the control group was observed by the 4.86 ± 1.4 days on the average, and by the 1.77 ± 0.41 days in the main group on the average ($p < 0.001$).

Emergence of the first granulation tissues and the speed of decrease in the wounds area are among the most important features of the wound process dynamics. In the control group, the granulation tissue emerged by the 7.65 ± 1.25 days on the average, and by the 4.79 ± 0.41 days in the main group ($p < 0.001$).

By the 5th day of the wound process, the index of L.N. Popova amounted to 2.53 ± 1.37 % on the average in the control group, and 3.19 ± 0.88 % in the main group ($p = 0.182$), and the index of V.S. Peschansky on the 5th day was 0.12 ± 0.069 mm^2 in the control group, and 0.159 ± 0.044 mm^2 in the main group ($p = 0.091$). By the 10th day of the course of the wound process, the index of L.N. Popova was equal to 2.71 ± 0.72 % in the control group, 3.61 ± 0.49 % in the main group ($p = 0,101$), and the index of V.S. Peschansky in the control group was equal to 0.194 ± 0.056 mm^2, while in the main group it was equal to 0.289 ± 0.039 mm^2, ($p = 0.04$). By the 15th day, in the control group the index of L.N. Popova was equal to 3.63 ± 0.81 %, while in the main group it was 5.23 ± 2.06 % ($p = 0.278$), and the index of V.S. Peschansky in the control group was 0.311 ± 0.071 mm^2, and in the main group it was 0.423 ± 0.099 mm^2, ($p = 0.183$).

The white blood cell count parameters are assumed to be one of the methods of the laboratory control of the inflammation process. The white blood cell count, determined on the 1st day of the patient's stay at the inpatient facility was equal to 11.62 ± $1.02 \cdot 10^9$/L in the control group, and in the main group it was 11.54 ± $1.07 \cdot 10^9$/L. The initial white blood cell count in both groups was statistically not distinguishable for patients with wounds of the same degree of lesion as classified by Wagner F.W. At the same time, the difference in the leucocytosis values in the initial period of the wound process is statistically not proven ($p = 0.654$).

By the fifth day of the wound process, the white blood cell count in the control group was 12.39 ± $3.58 \cdot 10^9$/L on the average, in the main group 10.86 ± $1.46 \cdot 10^9$/L ($p = 0.514$), leucocytosis more than $11 \cdot 10^9$/L in the control group was in the 47 (39.17 %) patients, and in the main group it was in the 28 (26.92 %) patients. The validity criterion p was 0.073. By the tenth day of the wound process, the leucocytosis level was 12.61 ± $2.44 \cdot 10^9$/L for the control group, and in the main group it was 8.52 ± 2.2·10/L (p = 0.215); leucocytosis was more than $11 \cdot 10^9$/L in the 30 patients (25 %) of the control group and in the 16 patients (15.4 %) of the main group ($p = 0.107$). By the fifteenth day of the wound process, the leucocytosis level in the control group was 7.75 ± $1.78 \cdot 10^9$/L, while in the main group it was 6.92 ± $0.58 \cdot 10^9$/L ($p = 0.922$), the leucocytosis level was more than $11 \cdot 10^9$/L in the control group was observed in the 11 patients (9.17 %), and in 2 patients (1.92 %) in the main group ($p = 0.043$).

One of the important parameters of the inflammation response of the body is the LII, which indirectly shows the presence or absence of the complicated course of the wound process. We were using the LII norm equal to 0.6–1.5, calculated by the Calf-Califa formula [1].

The initial level of LII (1st day), higher than 1.5 in the control group, was observed in the 75 (62.5 %) cases, while in the main group it was observed in the 63 (60.6 %) cases ($p = 0.875$). By the 5th day, the level of LII above the norm in the control group was observed in the 63 (52.5 %) cases, and in the main group – in the 47 (45.2 %) cases ($p = 0.339$). By the 10th day, the level of LII above the norm was observed in the 57 (47.5 %) patients of the control group, while in the main group the LII remained increased only in the 32 (30.8 %) ($p = 0.016$ by the χ^2 criterion). By the 15th day, the level of LII above the norm was observed in the 42 (35.0 %) patients of the control group, while in the main group the LII was within the norm in all patients ($p < 0.001$ by the χ^2 criterion).

Conclusion

Using exogenous nitrogen monoxide in the comprehensive treatment of necrotizing ulcerous complications of the diabetic foot syndrome makes it possible to achieve anti-inflammation effect and formation of the proper granulation tissue within earlier terms than under the traditional treatment.

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Received on May 07, 2013.