https://doi.org/10.33878/2073-7556-2022-21-1-89-98

Check-up and Treatment of Chronic Postoperative Wounds of the Anal Canal and Perineum

Svetlana V. Nekhrikova, Marina A. Sukhina, Olga A. Mainovskaya, Oksana Yu. Fomenko, Evgeny E. Zharkov, Roman Yu. Khryukin, Olga V. Tkalich, Alexander Yu. Titov

Ryzhikh National Medical Research Center of Coloproctology (Salama Adilya str. 2, Moscow, 123423, Russia)

ABSTRACT *AIM: to work out the algorithm for diagnosis and treatment of non-healing postoperative wounds of the perineum and anal canal.*

PATIENTS AND METHODS: the prospective cohort study included 119 people which underwent surgery for chronic anal fissure, hemorrhoids and anal fistula. The main group included 63 patients with long-term non-healing chronic wounds (46-159 days after surgery, mean 106.0 ± 44.8 days). The control group included 56 patients, whose postoperative period was uneventful and whose wounds healed on the 38.0 ± 10.4 days (p = 0.001). The wound healing and possible deviations in its course were assessed in all the patients using clinical, microbiological, cytological, pathomorphological pathophysiological tests, as well as molecular diagnostics (PCR). The main and control groups of the patients were homogenous in the main parameters (age, sex, the nature of surgical treatment), with the exception of the history of the disease. In the patients with a history of non-healing postoperative wounds, the incidence of sexually transmitted infections (STI) and inflammatory diseases of the pelvic organs, possibly caused by STI, was 44.4%, and in the patients of the control group — 10.7%, (p = 0.002).

RESULTS: in all patients of the main group at the time of admission and in 85.7% of the control group on the 30th day after the surgery, the wounds were contaminated with various microorganisms during bacteriological examination. Clinically significant microorganisms were found in 71.4% of the patients in the main group and in 12.5% of the control group (p = 0.0001). Associations of microorganisms were found in 73.0% in the main group and only in 33.9% in the controls (p = 0.01). During PCR in wounds of the perineum and anal canal STI were found in 34.9% in the main group, while in the control — 7.1% (p = 0.003). Histology of tissues taken from the area of non-healing wounds revealed papillomavirus infection (koilocytosis) in 11 (17.5%) patients. The patients with non-healing wounds were treated depending on the isolated pathogen and sensitivity to antibiotics, as well as appropriate treatment if an STI was detected. In 6.3% in the main group, the wounds did not heal and a spasm of the internal sphincter was detected. These patients got injection of botulinum toxin type A (BTA) into the internal sphincter (40 U). After 9.4 days after the BTA complete wound healing was noted. A control test (profilometry) on the 7th day after the BTA showed no spasm of the internal sphincter in all cases.

CONCLUSION: healing in patients after anal surgery may slow down due to the presence of infectious agents, opportunistic pathogens and STI, which support the inflammatory wound reaction in the postoperative period, as well as due to spasm of the anal sphincter. It is necessary to carry out targeted diagnostics, to prescribe appropriate treatment, and in the presence of anal sphincter spasm, to eliminate it.

KEYWORDS: *long-term non-healing, chronic wounds, opportunistic pathogenic clinically significant microorganisms, STIs, spasm of the internal sphincter, botulinum toxin type A.*

CONFLICT OF INTEREST: *The authors declare no conflict of interest*

FOR CITATION: Nekhrikova S.V., Sukhina M.A., Mainovskaya O.A., Fomenko O.Yu., Zharkov E.E, Khryukin R.Yu., Tkalich O.V., Titov A.Yu. Check-up and Treatment of Chronic Postoperative Wounds of the Anal Canal and Perineum. *Koloproktologia.* 2022;21(1):89–98. (in Russ.). https://doi.org/10.33878/2073-7556-2022-21-1-89-98

ADDRESS FOR CORRESPONDENCE: *Nekhrikova S.V., Ryzhikh National Medical Research Center of Coloproctology, Salama Adilya str. 2, Moscow, 123423, Russia, e-mail: nehrikova@yandex.ru*

Received — 08.12.2021 *Revised — 19.01.2022* *Accepted for publication — 08.03.2022*

INTRODUCTION

Treatment of long-term non-healing wounds remains one of the urgent problems of healthcare to date [1–4]. Long-term non-healing, so-called chronic wounds occupy a special place in surgery [5,6]. The issues of check-up and treatment of chronic wounds include not only a medical component, but also an ethical one, which is of great importance in modern conditions [7]. Often patients with non-healing wounds make claims about why the wound has not healed within the time specified by the doctor, which, in their opinion, may be due to inadequate surgery.

According to the European Society for Tissue Repair, "a wound that does not heal for a period that is normal for wounds of this type or location should be considered chronic" [8].

In our opinion, if the wound healing after anal and perineal surgery is delayed for over 45 days, this indicates the chronic process (the long-term non-healing wound) [7,9].

There may be several etiological factors of the transformation of a wound into a long-term non-healing one. Currently, the authors point to the possibility of a negative effect on the wound healing of spasm of the sphincter, which may develop in the postoperative period. The spasm of the anal sphincter, in turn, blocks the healing of wounds and promotes the transition of the latter into long-term non-healing [10].

The conditions for the formation of a long-term non-healing wound are also the presence of a chronic persistent infection [6,11]. Various microorganisms and their associations are found in the wounds of the perineum after surgery. These are opportunistic bacterial pathogens, which can acquire pathogenic properties. Among conditionally pathogenic microorganisms, a special clinically significant group isdistinguished [7,9]. Clinically significant microorganisms can cause nosocomial infections under certain conditions and have increased antibiotic resistance [7,9].

Sexually transmitted infections (STIs) can be attributed to another group, which can also be found in wounds after anal surgery [7,9,12].

Currently, the incidence of sexual infections is steadily increasing worldwide [13–16]. STIs often turn into a chronic form. This is primarily due to the scant clinical manifestations of sexually transmitted infections. STIs are often have slightly symptomatic or even asymptomatic manifestations, so many patients do not go to the doctor in a timely manner, or do self-medication [13,17].

The issues of check-up and treatment of patients with non-healing wounds in coloproctology have not been studied to date. Publications that relate to this topic are practically not found in the literature.

In connection with the above, this study had the aim to identify, check-up and treat patients with chronic, long-term non-healing wounds after operations on the perineum and anal canal.

PATIENTS AND METHODS

A prospective cohort study has been conducted since 2018 to the present.

Inclusion criteria for patients:

1. Age 18–75 years;
2. Wounds after general proctological surgeries;
3. Outpatient cohort;
4. Consent to participate in the clinical trial.

Exclusion criteria:

1. Refusal of the patient from the trial;
2. The occurrence of a life-threatening condition (acute profuse bleeding, myocardial infarction, acute cerebrovascular accident, Quincke's edema, anaphylactic shock, as well as any condition that required the transfer of the patient to the intensive care unit);
3. IBD, malignant tumors of any location.

One-hundred-nineteen patients were prescreened for inclusion in the study. These patients met the inclusion criteria, there were no exclusion criteria at the time of screening. All 119 patients included: the main group of 63 patients who showed long-term non-healing wounds of the perineum and anal canal, and the control group of 56 patients in whom the wound process was without any deviations.

All the patients of the main and control groups underwent surgery for hemorrhoids, anal fistulas, and chronic anal fissures.

In the patients of the main group, 106.0 ± 44.8 (46–159) days have passed after surgery. In the control group, the wounds were completely epithelized by the 30th day after surgery.

On the 38.0 ± 10.4 day after surgery, in the patients of the control group, wounds healed with the formation of a connective tissue scar ($p = 0.001$).

The patients in both groups were aged about 40 years (42.3 ± 11.5 in the main group and 41.3 ± 11.8 years in control one; ($p = 0.74$). No prevalence in gender was found in both groups (33 females in the main group vs 30 — in the control; $p = 0.9$).

The patients of the main group in 32 (50.8%) cases were operated on for chronic anal fissures with sphincter spasm vs 25 (44.6%) — in the controls ($p = 0.69$); for hemorrhoids — 17 (27.0%) vs 16 (28.6%) patients ($p = 0.84$); for anal fistulas — 14 (22.2%) vs 15 (26.8%) ($p = 0.58$).

Patients with anal fissures underwent fissurectomy. This procedure was supplemented by lateral subcutaneous sphincterotomy in 18 (26.8%) patients of the main and in 15 (26.8%) patients of the control groups) or botulinum toxin type A injection (14 vs 10, respectively, $p = 1.0$).

Patients with intersphincteric or trans-sphincteric anal fistulas with the involvement of a subcutaneous part of the external sphincter underwent fistulectomy: 11 (17.5%) patients of the main and 10 (17.9%) of the control group ($p = 1.0$). Fistulectomy with the reconstruction of the sphincter was done in 6 (9.5%) cases of the main group and in 5 (8.9%) — in the control one ($p = 1.0$).

Thus, both groups were homogeneous in gender, age, nosology and type of surgery.

However, an analysis of the life history showed that 28 (44.4%) patients of the main group had sexually transmitted infections, as well as inflammatory diseases of the reproductive system that could be caused by STIs.

At the same time, only 6 (10.7%) patients of the control group noted that they were treated for STIs and diseases that could be caused by them ($p = 0.002$).

The wound healing and possible deviations in its course were evaluated in all the patients using clinical, microbiological, cytological, pathomorphological pathophysiological tests, as well as molecular diagnostics (PCR).

In order to reveal opportunistic bacterial pathogens contaminating wounds and the rectum, bacteriology was done in the postoperative period. The polymerase chain reaction (PCR) method was used to detect STIs in the wounds discharge and in rectum.

To track the changes of the wound healing in the patients of both groups, cytological and pathomorphological tests of cell and tissue cultures from postoperative wounds were carried out. The presence or absence of spasm of the internal anal sphincter was checked by profilometry. All examinations were carried out in the patients of the main group during primary consultation for a non-healing wound and then on the 14th day from the onset of the treatment; in the patients of the control group — on the 30th day after surgery.

RESULTS

In all of the patients of the main group and 85.7% of the control one, postoperative wounds were contaminated with various microbes during treatment. It should be emphasized that in 8 (14.3%) patients of the control group there was no bacterial growth ($p = 0.006$).

In patients of both groups, E. coli prevailed: 34 (54.0%) patients of the main group vs 32 (57.1%) controls ($p = 0.46$).

However, Enterococcus faecal is was significantly more common in the patients of the main group compared with the control group: 19 (30.2%) vs 6 (10.7%) ($p = 0.04$).

Staphylococcus aureus was detected in 8 (12.7%) patients of the main group and in 1 (1.8%) patient of the control group ($p = 0.03$). Proteus mirabilis was detected in 7 (11.1%) patients of the main and was not detected in the control one ($p = 0.01$).

Opportunistic bacterial pathogens such as Staphylococcus haemolyticus and Klebsiella pneumoniaewere revealed in 6 (9.6%) cases in the patients of the main group. Streptococcus

Table 1. *Microflora of discharge in patients of the main and control groups in the postoperative period*

Microorganisms	Main Group 106 days after surgery	Control Group 30th day after surgery	p
Escherichia coli	34 (54.0%)	32 (57.1%)	0.85
Proteus mirabilis	7 (11.1%)*	0 (0%)*	0.01
Enterobacter cloacae	11 (17.5%)	8 (14.3%)	0.80
Enterococcus avium	2 (3.2%)	2 (3.6%)	1.0
Enterococcus faecium	8 (12.7%)*	1 (1.8%)*	0.04
Enterococcus faecalis	19 (30.2%)*	6 (10.7%)*	0.04
Corynebacterium amycolatum	1 (1.6%)	0 (0%)	1.0
Staphylococcus epidermidis	11 (17.5%)	10 (17.9%)	1.0
Staphylococcus haemolyticus	3 (4.8%)	0 (0%)	0.25
Staphylococcus aureus	8 (12.7%)*	1 (0%)*	0.04
Streptococcus pyogenes Streptococcus mitis	3 (4.8%) 1 (1.6%)	0 (0%) 0 (0%)	0.25 1.0
Streptococcus anginosus Streptococcus agalactiae	2 (3.2%) 1.6	2 (3.6%) 1 (1.8%)	1.0 1.0
Pseudomonas fragi Pseudomonas luteola	1 (1.6%) 1 (1.6%)	0 (0%)	1.0 1.0
Citrobacter freundii Citrobacter braakii	2 (3.2%) 1 (1.6%)	1 (1.8%) 0 (0%)	1.0 1.0
Serratia rubidaea	1 (1.6%)	0 (0%)	1.0
Morganella morganii	1 (1.6%)	0 (0%)	1.0
Klebsiella pneumoniae Klebsiella oxytoca	3 (4.8%) 1 (1.6%)	0 (0%) 1 (1.8%)	0.25 1.0
Associations of conditionally pathogenic microorganisms	46 (73.0%)*	19 (33.9%)*	0.01
No growth	0*	8 (14.3%)*	0.006

** $p < 0.05$*

pyogenes, which belongs to pathogenic microorganisms, was detected in 3 (4.8%) patients of the main group (p = 0,25).

In the patients of the control group, all of the above microorganisms were not found in postoperative wounds, which was confirmed by bacteriology.

The detection rate of opportunistic bacterial pathogens (Enterococcus faecalis, Enterococcus faecium, Staphylococcus aureus, Proteus mirabilis, Klebsiella pneumoniae) in the patients of the main group was 71.4%. In the patients of the control group, Staphylococcus aureus, Proteus mirabilis, Klebsiella pneumoniae were not detected in all cases. Clinically significant microbes in the patients of the control group were represented by enterococci (Enterococcus faecalis, Enterococcus faecium) and were found only in 7 (12.5%) cases (p = 0.0001).

The bacteriology also revealed that in 46 (73.0%) cases in main group, opportunistic bacterial pathogens were associated with each other. Thus, four infections were detected at once in 2 (3.2%), 3 infections — in 11 (17.5%) patients of the main group. A combination of two microorganisms was detected in 33 (52.4%) patients with non-healing wounds. In the control group, significantly less often — in 19 (33.9%) patients, an association of two conditionally pathogenic microorganisms was detected (p = 0.01) (Table 1).

PCR in samples from postoperative wounds showed STIs in 22 (34.9%) patients of the main group and in 4 (7.1%) patients of the control (p = 0.003) (Fig.1).

Ureaplasma urealyticum was detected in 5 (7.9%) patients of the main group and in one in controls (1.8%). Cytomegalovirus (CMV) was detected in 6 (9.5%) patients of the main group, whereas in the control group — only in one (1.8%).

Candida albicans was revealed in 3 (4.8%) cases and Gardnerella vaginalis — in 3 (4.8%) females and were somewhat less common in non-healing wounds in the patients of the main group. In the control group, only one (1.8%) female patient had Gardnerella vaginalis in the postoperative wound and one male patient (1.8%) had Candida albicans. Ureaplasma parvum (ureaplasma parvum) was diagnosed in 2 (3.2%) female patients of the main group and was not found in any observation in the patients of the control

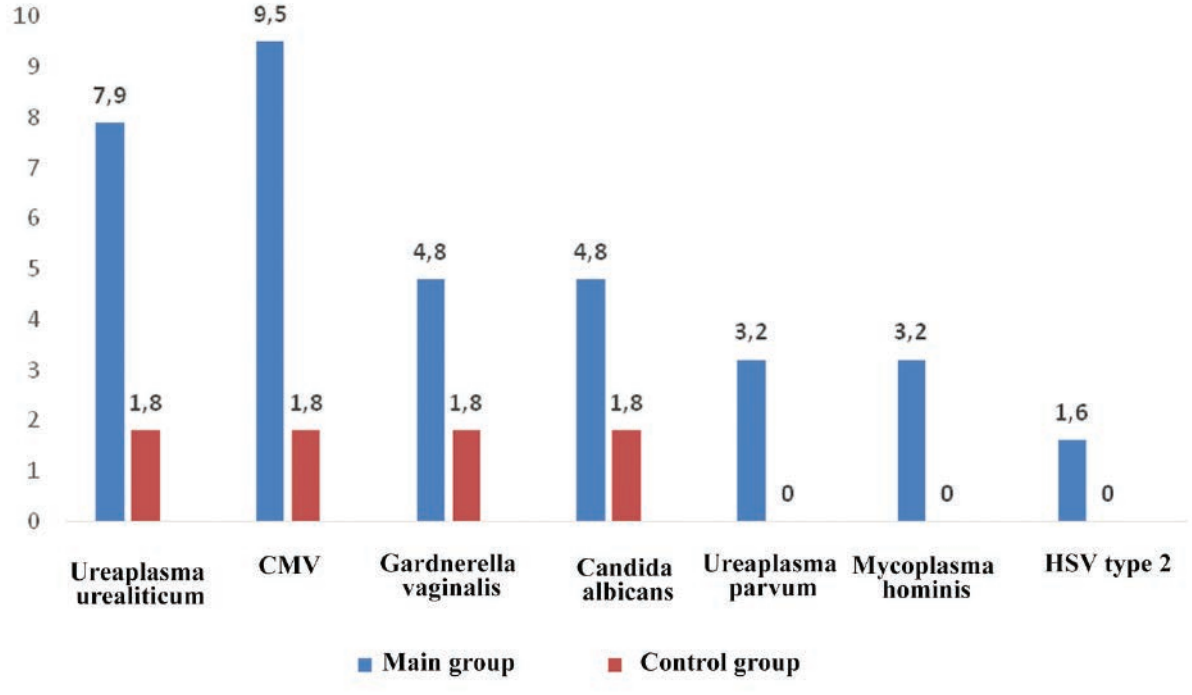

Figure 1. *Frequency of STIs in patients of the main and control groups*

group. Mycoplasma hominis was detected in two (3.2%) cases — in a male and a female of the main group. Herpes simplex virus (HSV) type 2 or genital herpes was detected in one (1.6%) female patient of the main group (Fig.1).

Indications in the history of STIs in the past and diseases of the pelvic organs that could be caused by them were available in 15 (23.8%) of 22 (34.9%) with diagnosed STIs in the postoperative period in the patients of the main group with chronic wounds. This fact may indicate the existence of a smoldering inflammatory process in the genitals, which has not been fully treated and has passed into a chronic form. At the same time, the detection of STIs is extremely difficult if there is no provoking factor. The presence of wounds in the anal canal and perineum is the most of them. STIs can create favorable conditions for the reproduction of opportunistic bacterial pathogens. The latter, in turn, maintaining a long-existing phase of inflammation, slow down the processes of healing.

During cytology of smears-prints in 37 (58.7%) patients with non-healing wounds, the picture of chronic inflammation with the presence of leukocytes (neutrophil granulocytes) prevailed: from 60–100 or more cells in the area of vision — in 17 (27.0%), from 25 to 50 in the area of vision — in 13 (20.6%), from 10 to 20 — in 7 (11.1%) patients. Against the background of a weakly expressed phagocytic reaction of neutrophils, various microflora was found in large or moderate amounts. Microorganisms were found both outside and inside the cells, while phagocytosis was often incomplete. And also, in 23 (36.5%) patients of the main group in smears-prints from wounds, multinucleated cells of alien bodies type were observed. By the 30th day of the postoperative period, neutrophils with signs of dystrophy were detected in all the patients of the control group in a small amount — from 1 to 10 in the area of vision, ($p < 0.0001$).

All the patients underwent biopsy from the area of postoperative wounds. At the same time, there was a correlation between the data of pathomorphological and cytological tests. In 35 (55.5%) patients of the main group, excessive scar tissue was detected in the biopsy: hyperkeratosis — in 21 (33.3%), parakeratosis — in 14 (22.2%) cases. Lymphoid infiltration as detected in 32 (50.8%) patients: severe and moderate in 26 (41.3%), weak — in 6 (9.5%). In 11 (17.5%) patients, a histology from the area of non-healing wounds revealed koilocytosis. The appearance of koilocytes — cells with enlarged deformed nuclei, the division process of which is disrupted, indicates a past papillomavirus infection [18]. In all 56 patients of the control group, single, dystrophically altered leukocytes, as well as macrophages and fibroblasts in small amounts ($p < 0.0001$) were detected in the biopsy.

All the patients of the main and control groups underwent profilometry. At the same time, spasm of the internal sphincter was detected in 4 (6.3%) patients of the main group. STIs were detected in 3 (4.8%) of them: Ureaplasma urealyticum (1.6%) — in one case, Herpes simplex virus type 2 — in one (1.6%) female and Gardnerella vaginalis also in one (1.6%) female patient.

Treatment

The patients of the main group were prescribed treatment aimed at activating reparative processes. The type of pathogen was taken into account, as well as the sensitivity of the isolated microorganism to antibiotics. When STIs were detected in combination with opportunistic bacterial pathogens, a complex treatment was prescribed.

To sanitize the wound, in addition to the treatment that promotes the suppression of opportunistic bacterial pathogens, medications aimed at eliminating STIs were prescribed.

When mycoplasma hominis, ureaplasma urealiticum and ureaplasma parvum were detected, antibiotics (macrolides, tetracyclines, fluoroquinolones) were prescribed for 7 days. The patients diagnosed with gardnerellosis received agents with antiprotozoal and antimicrobial effects (metronidazole, tinidazole, ornidazole) for 4–5 days. Candidias is was treated with antimycotic drugs from the triazole, imidazole, polyene, and allylamine groups (treatment was carried out for 5–7 days). For genital herpes, agents with interferon-inducing activity,

viral nucleic acid replication inhibitors, pyrophosphate analogues were prescribed for 5 days. Cytomegalovirus infection was treated with antiviral, immunomodulatory agents for 5–10 days.

After the complex therapy in 59 (93.7%) patients of the main group, the wounds healed completely with the formation of a connective tissue scar. However, in 4 (6.3%) patients of the main group who developed spasm of the internal sphincter in the postoperative period (it was confirmed by profilometry), the wounds did not heal. Although, against the background of the treatment for non-healing wounds, positive changes were observed (reduction of wound size, decreased pain, cessation or reduction of blood or blood discharge from the wound area). These patients required additional treatment: botulinum toxin type A (BTA) injection into the internal sphincter [10,19,20].

BTA was injected as follows: 10 units at 4 points of the internal sphincter at 1,5,7 and 11 o'clock (a total of 40 units) [10]. On average, on the 9.4 day after the BTA treatment, the patients with spasm of the internal sphincter showed complete wound healing with the formation of a postoperative scar. They underwent a control examination on the 7th day after the BTA injection. At the same time, spasm of the internal sphincter was not detected in any observation.

DISCUSSION

Treatment of chronic wounds remains one of the serious problems in medicine [1–3]. According to our data, the wound healing after anal surgery is considered chronic, existing for more than 45 days without signs of active healing [4,7]. Various microbes and their associations were found in the wounds of the perineum after surgery. They belong to opportunistic bacterial pathogens, which can acquire pathogenic features. Among them, a special clinically significant group was distinguished [7,9]. Sexually transmitted infections (STIs) can also be found in wounds after anal surgery [7,9,12].

Publications that relate to this topic are practically not found in the literature. This was the subject of this very study.

The results obtained indicate that 44.4% of patients in the main group had STIs in the past, as well as inflammatory diseases of the reproductive system that could be caused by STIs.

In the control group, only 10.7% of patients noted STIs and diseases that could be caused by these infections in lifetime ($p = 0.002$).

In all patients of the main group, some kind of microorganism was detected, and in 14.3% of the control group, the samples were sterile ($p = 0.006$). Such clinically significant microorganisms as enterococci (Enterococcus faecalis, Enterococcus faecium), Staphylococcus aureus, proteus mirabilis and Klebsiella (Klebsiella pneumoniae) were detected in 71.4% of patients in the main group. In patients of the control group, clinically significant microorganisms represented by enterococci (Enterococcus faecalis Enterococcus faecium) were detected only in 12.5% of cases ($p = 0.0001$). Associations of microorganisms in bacterial cultures were detected in 73.0% of patients with non-healing wounds, in the control group — only in a third of patients ($p = 0.01$). In the main group 34.5% of patients were diagnosed with various STIs, whereas in the control group — only in 7.1% ($p = 0.003$). The quarter of patients who were found to have STIs during examination in the postoperative period had already suffered STIs or diseases that could be caused by these infections in the past.

During cytology, 36.5% of patients in the main group had a picture of "perverted" healing (the presence of multinucleated cells of the alien bodies type in smears-prints from wounds), as well as 58.7% had a chronic inflammatory process with the presence of unchanged leukocytes (neutrophil granulocytes). In all patients of the control group, by day 30, leukocytes with dystrophy phenomena were in small numbers and did not exceed 10 in the area of vision, ($p < 0.0001$).

In 11 (17.4%) patients, histology from the area of non-healing wounds revealed koilocytosis, which indicates a past papillomavirus infection [18].

Patients with long-term non-healing wounds were prescribed appropriate treatment depending on the isolated pathogen, taking into account sensitivity to antimicrobial agents, and if STIs are detected, treatment aimed at suppressing STI. However, in 6.3% of patients of the main group, in whom a spasm of the internal anal sphincter was detected during profilometry at the time of treatment for chronic wounds, the wounds did not heal against the background of antimicrobial treatment, although positive changes were observed. Currently, the injection of botulinum toxin type A is a modern and effective method of eliminating anal spasm of the anal sphincter [10,20].

These patients required additional injection of botulinum toxin type A (BTA) into the internal sphincter in a total dosage of 40 units, according to the original technique [10]. On average, on the 9.4 day after the BTA injection, patients with spasm of the internal sphincter showed complete wound healing with the formation of a postoperative scar. They underwent a control test on the 7th day after the BTA injection. At the same time, spasm of the internal sphincter was not detected in any case.

CONCLUSION

In patients with long-term non-healing wounds of the anal canal and perineum, the healing is slowed down due to contamination of wounds by various microorganisms: opportunistic bacterial pathogens, including clinically significant, as well as sexually transmitted infections. All these infectious agents support the inflammatory wound response, slowing the healing of wounds in the postoperative period. Also, in patients with chronic wounds, functional diagnostics (profilometry) is necessary in order to eliminate anal spasm of the internal sphincter.

AUTHORS CONTRIBUTTON

Concept and design of the study: *Svetlana V. Nekhrikova, Alexander Yu. Titov*

Collection and processing of the material: *Svetlana V. Nekhrikova, Marina A. Sukhina, Olga A. Mainovskaya, Evgeny E. Zharkov, Oxana Yu. Fomenko, Roman Yu. Khryukin, Olga V. Tkalich*

Statistical processing: *Svetlana V. Nekhrikova, Evgeny E. Zharkov*

Editing: *Alexander Yu. Titov*

INFORMATION ABOUT THE AUTHORS (ORCID)

Alexander Yu. Titov — MD, Head of General and Reconstructive Coloproctology Unit of RNMRC of Coloproctology of Health Ministry of Russia; ORCID 0000-0002-1636-8075

Svetlana V. Nekhrikova — candidate of medical sciences, coloproctologist of General and Reconstructive Coloproctology Unit of RNMRC of Coloproctology of Health Ministry of Russia; ORCID 0000-0002-2815-4808

Evgeny E. Zharkov — candidate of medical sciences, junior researcher of General and Reconstructive Coloproctology Unit of RNMRC of Coloproctology of Health Ministry of Russia; ORCID 0000-0003-3403-9731

Marina A. Sukhina — candidate of biological sciences, Head of Microbiological and Immunological Research Unit of RNMRC of Coloproctology of Health Ministry of Russia; ORCID 0000-0003-4795-0751

Olga A. Mainovskaya — candidate of medical sciences, Head of Pathomorphology and Immunohistochemical Research Unit of RNMRC of Coloproctology of Health Ministry of Russia; ORCID 0000-0001-8189-3071

Oksana Yu. Fomenko — MD, associate professor, Head of Clinical Pathophysiology Laboratory of RNMRC of Coloproctology of Health Ministry of Russia ORCID 0000-0001-9603-6988

Olga V. Tkalich — doctor of consultative polyclinic of RNMRC of Coloproctology of Health Ministry of Russia; ORCID 0000-0002-2378-9871

Roman Yu. Khryukin — postgraduate of General and Reconstructive Coloproctology Unit, doctor of consultative polyclinic of RNMRC of Coloproctology of Health Ministry of Russia; ORCID 0000-0003-0556-1782

REFERENCES

1. Vinnik Yu.S., Markelova N.M., Tyuryumin V.S... Modern methods for treatment of purulent wounds *Siberian Medical Review*. 2013;1:18–24. (in Russ.).

2. Lewis S. Pilcher. *The Treatment of Wounds*. 2015:10–15.

3. Frolov S.A., Kuzminov A.M., Vyshegorodtsev D.V., Korolik V.Yu., et al. Low-temperature argon plasma in the wounds treatment after hemorrhoidectomy. *Koloproktologia*. 202;20(3):51–61. (in Russ.).

4. Sheets AR, Massey CJ, Cronk SM, Iafrati MD, Herman IM.Sheets AR, et al. J Matrix- and plasma-derived peptides promote tissue-specific injury responses and wound healing in diabetic swine. *Transl Med*. 2016;Jul 214(1):197.

5. George Han 1 , Roger Ceilley Chronic Wound Healing: A Review of Current Management and Treatments. *Adv Ther*. 2017;Mar 34(3):599–610.

6. Potekaev N.N., Frigo N.V.,Michenko A.V., Lvov A.N., Panteleev A.A., Kitaeva N.V. Chronic ulcers and wounds of the skin and subcutaneous tissue that do not heal for a long time. *Clinical Dermatology and Venereology*. 2018;17(6):7–12. (in Russ.).

7. Nekhrikova S.V., Titov A.Yu., Korneva T.K., Markova E.V., Vorobieva I.V. Treatment of non-healing wounds of the perineum and anal canal. *RMZh*. 2014;17:1242 -1247. (in Russ.).

8. Obolensky V.N. Modern methods of treating chronic wounds. *Surgery*. 2016;10: 148-154. (in Russ.).

9. Nekhrikova S V, Titov A Yu, Kashnikov V N, Romanov R I, Veselov A V. Anal canal and perianal diseases treatment in an outpatient setting. *Evidence-Based Gastroenterology*. 2019;8(3):27–37. (in Russ.).

10. Tkalich O.V., Ponomarenko A.A., Fomenko O. Yu., Arslanbekova K.I., Khryukin R.Yu., Misikov V.K., Mudrov A.A., Zharkov E.E. The treatment of chronic anal fissures with fissure excision and botulinum toxin type A injection (ISRCTN97413456). *Koloproktologia*. 2020;19(1):80–99. (in Russ.).

11. Ribeiro DML, Carvalho Júnior AR, Vale de Macedo GHR, Chagas VL, et al. Polysaccharide-Based Formulations for Healing of Skin-Related Wound Infections: Lessons from Animal Models and Clinical Trials. *Biomolecules*. 2019;Dec 3010(1):63

12. Nekhrikova, S. Chronic wounds perineum and anal canal. *Colorectal Disease. (ESCP), Berlin*.2017;19(Suppl.2):33.

13. Khairullina G.A., Konovalov A.S., Zueva A.G., Surovtsev V.V., Khodyakov A.V. Prevalence of sexually transmitted infections, *Difficult patient*..2018;16(6):67–70. (in Russ.).

14. Wagenlehner Florian M.E. , Brockmeyer N.H., Thomas Discher, Klaus Friese, et al. The Presentation, Diagnosis, and Treatment of Sexually Transmitted Infections. *Dtsch Arztebl Int*. 2016;Jan 11;113(1-02):11–22.

15. Marin V, Bertoncello C.Marin V, et al. Sexually transmitted diseases: epidemiological and social aspects. *Ann Ig*. 2002;Mar-Apr;14(2):163–9.

16. McMurray M, Armstrong M, Paulson J. Addressing the Increased Incidence of Common Sexually Transmitted Infections *J Am Osteopath Assoc*. 2018;Aug 1;118(8):51–55.

17. Jensen JS, Cusini M, Gomberg M, Moi H.Jensen JS, et al. 2016 European guideline on Mycoplasma genitalium infections. *J Eur Acad Dermatol Venereol*. 2016;Oct 30(10):1650–1656.

18. Ershov V.A., Vyazovaya A.A., Narvskaya O.V. Immunomorphological criteria for coylocytes. *Bulletin of St. Petersburg State University*. 2014;2:171–174. (in Russ.).

19. Khryukin R.Yu. 1, Kostarev I.V. 1, Arslanbekova K.I. 2, Nagudov M.A. 1, Zharkov E.E. Botulinum toxin

type A and lateral subcutaneous sphincterotomy for chronic anal fissure with the sphincter spasm. What to choose? (systematic literature review and meta-analysis). *Koloproktologia*. 2020;19(2):113–128. (in Russ.).

20. Shelygin Yu.A., Tkalich O.V., Ponomarenko A.A. Follow-Up Results of Combination Treatment of Chronic Anal Fissure. *International Journal of Pharmaceutical Research*. 2020;12(2):244–249.