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Results of chronic anal fissure treatment with botulinum toxin type A at a dose (dosage) of 80 units without its incision (single-center prospective randomized controlled trial NCT05598164)

Karina I. Sagidova[1], Maria A. Ignatenko[1], Evgeny E. Zharkov[1], Aleksey A. Ponomarenko[1], Ekaterina Yu. Lebedeva[1], Ivan V. Kostarev[1,2], Andrey A. Mudrov[1,2]

[1]Ryzhikh National Medical Research Center of Coloproctology (Salyama Adilya st., 2, Moscow, 123423, Russia)
[2]Russian Medical Academy of Continuous Professional Education (Barrikadnaya st., 2/1, bld. 1, Moscow, 125993, Russia)

ABSTRACT *AIM: to assess efficacy of botulinum toxin type A (BTA) at a dosage of 80 units for chronic anal fissure (CAF) without excision.*

PATIENTS AND METHODS: single-center prospective randomized controlled trial (NCT05598164) was held between September 2022 and December 2024 in order to compare isolated usage of BTA (main group) at a dosage of 80 units with its combination with excision of the fissure — BTA + EF (control group) for CAF. One hundred sixty-seven were randomized — 86 were included in main group and 81 — in control one. After application of exclusion criteria 126 patients were included in final analysis: 65 in group of BTA only and 61 in group of its combination with EF. Control examination, pain syndrome intensity according to visual-analogue scale (VAS), profilometry and assessment of transitory anal incontinence according to Wexner scale were done in pre- and postoperative period. The primary endpoint was epithelization of defect (for the main group) or postoperative wound (for the control group) on 60th day after surgery.

RESULTS: on the 60th day postoperative defect healed in 46/59 (78.0%; 95% confidence interval (CI): 65.2–87.7) patients in main group vs. 34/50 (68.0%; 95% CI: 53.3–80.5) patients for postoperative wound in control group (p = 0.3). At the same time, on the 15th day defect healed in 12/65 (18.4%) patients in BTA group, whereas no one's postoperative wound healed in group BTA + EF (p = 0.0003); on the 30th day — in 18/59 (30.5%) vs. 1/53 (1.9%) patients(p < 0,0001); on the 45th day — in 31/57 (54.4%) vs. 3/52 (5.8%) patients(p < 0.0001). The rate of postoperative complications was 23/65 (35.4%) in main group and 23/61 (37.7%) in controls (p = 0.8). On the 30th day transitory anal incontinence was detected in 15/60 (25.0%) patients in BTA group and in 18/53 (34.0%) in combinations of its injection with EF (p = 0.3); on the 60th day — in 7/60 (11.7%) and 9/51 (17.6%) patients (p = 0.4); external hemorrhoids thrombosis developed in 2/65 (3.1%) patients of main group and in 2/61 (3.3%) of control group (p = 1.0); intrasphincter fistula — in 5/60 (8.3%) and 3/50 (6.0%) patients (p = 0.7). Intensity of pain syndrome during the day and while defecation began to decrease in patients of main group from the 1st day after surgery, whereas it increased and returned to pre-operative level in control group by the 3d day, where remained till the 9th day, only after this it decreased. Significant differences between groups were revealed to 48–49th days. According to profilometry, spasm of internal anal sphincter (IAS) remained in 22/56 patients of main group and in 16/52 patients of control group; on 60th day — in 22/52 (39.3%) and 8/50 (16.0%) patients relatively (p = 0.004). In group of BTA there were statistically significantly fewer days of disability than in group of combination BTA with EF — 7 (6; 15) vs. 20 (15; 30) days. Method of treatment BTA + EF became significant factor, increasing chances of no epithelization on the 30th (odds ratio (OR) = 22.8; 95% CI: 2.93–178.0; p = 0.003) and 45th (OR = 19.5; 95% CI: 5.43–69.8; p < 0.0001) days. On the 60th day presence of IAS spasm was statistically significantly associated with non-healing (OR = 2.68; 95% CI: 1.08–6.66; p = 0.034). The factors which could influence the existence of transitory anal incontinence, were not detected.

CONCLUSION: refusal from EF while BTA's use at a dosage of 80 units allows to achieve defect epithelization on early post-operative period, lower intensity of pain syndrome and significantly decrease time of temporary disability.

KEYWORDS: *chronic anal fissure, CAT, botulinum toxin type A, BTA, excision of the fissure, spasm of the internal anal sphincter, inkobotulinum toxin*

CONFLICT OF INTEREST: *the authors declare no conflict of interests*

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ADDRESS FOR CORRESPONDENCE: *Karina I. Sagidova, Ryzhikh National Medical Research Center of Coloproctology, Salyama Adilya st., 2, Moscow, 123423, Russia; e-mail: karinaibakovna@gmail.com*

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INTRODUCTION

Hyper-tonus of the internal anal sphincter (IAS) plays a leading role in the pathogenesis of chronic anal fissure (CAF), which necessitates its elimination as part of therapeutic tactics [1]. One of the promising sphincter-sparing relaxation methods in the IAS today is the use of botulinum toxin type A (BTA). The effectiveness of this technique in randomized trials reaches 96%, which is a worthy alternative to lateral (subcutaneous) internal sphincterotomy (LIS) [2–4]. Most of studies focus on the isolated elimination of spasm of the internal anal sphincter [5], in turn, in Russian practice, the method is supplemented by excision of the defect, considering this a mandatory step. Nevertheless, according to the recent results of a study by N.A. Goloktionov et al., 2023 [6], avoiding fissure excision significantly improved early postoperative period. We also decided to do our own randomized trial on the treatment of CAF using botulinum toxin without excision.

PATIENTS AND METHODS

In the period from September 2022 to December 2024, a single-center prospective randomized controlled trial (NCT05598164) was done for comparing the isolated use of BTA (the main group) — incobotulotoxin A, at a dosage of 80 units with its combination with fissure excision — BTA + FE (the control group) in the treatment of CAF. Randomization was carried out using the random number generation method in Access (Microsoft Office 2013) 1:1 — when a patient was entered in the database, in case of an even number, he/she was assigned to the main group, and in case of an odd number, to the control group. A total of 167 patients diagnosed with CAF were randomized during this period. Eighty-six were included in the main group and 81 in the control group. Subsequently, 41 patients were excluded due to intraoperatively detected anal fistula (4 in the main and 6 in the control group); non-compliance with postoperative recommendations (3 people in each group), as well as due to non-attendance at

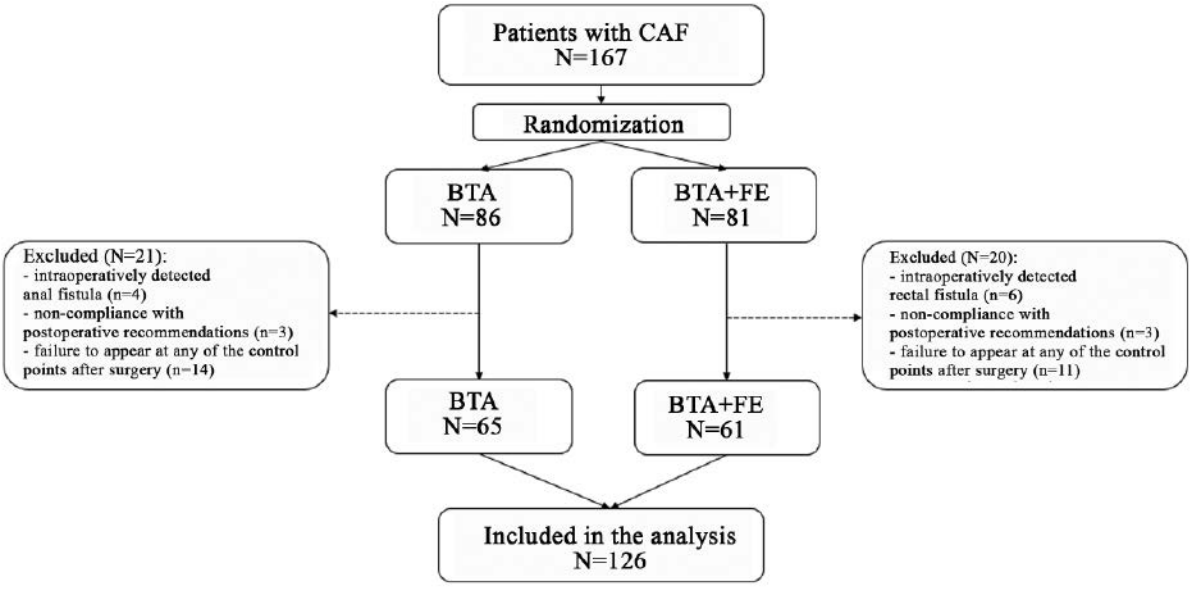

Figure 1. *Block chart of the research*

any of the control points after surgery (14 — in the main and 11 — in the control group). Thus, the final analysis included 126 patients: 65 in the group of isolated use of BTA and 61 in combination with FE (Fig. 1).

The diagnosis of 'Chronic anal fissure' was made if the patient had at least 1 of the following characteristics: a medical history of more than 2 months; cicatricial change of the lesion edges; fibrous polyp of the anal canal at the proximal edge of the lesion; the presence of a sentinel skin tag at the distal edge of the anal canal.

Inclusion Criteria

Established diagnosis of 'Chronic anal fissure' with confirmed spasm of the internal anal sphincter according to profilometry results; age of patients at least 18 years; signed informed consent to participate in the study.

Criteria for Non-inclusion

Individual intolerance and hypersensitivity to botulinum toxin; patients who have previously undergone anal canal surgery (with the exception of minimally invasive techniques); anal sphincter insufficiency (ASI) of any degree (over 0 point on Wexner's scale); pectenosis; fibrotic polyp of the anal canal or sentinel skin tag, accompanied by clinical manifestations; the patient has inflammatory diseases of the large intestine; anal fistula; the presence of severe somatic diseases in the stage of decompensation; pregnancy and lactation; myasthenia and myasthenic syndromes; external and internal hemorrhoids of stages II–IV, requiring combined surgery.

Exclusion Criteria

The presence of a fissure complicated by a fistula during intraoperative rectal revision; the patient's refusal to participate at any stage of the study; non-compliance with postoperative recommendations; the patient's failure to attend any of the control points or the absence of any contact with him/her.

Methods of Examination of Patients

As part of the study, all patients underwent profilometry using a Solar GI HRAM device (the Netherlands) before surgery, as well as on the 30th and 60th days after the surgery. The spasm of the internal anal sphincter was confirmed by exceeding the upper limit of the normal value of one of two parameters — the average pressure in the anal canal at rest (normal values: 44.0–60.4 mm Hg) or the maximum pressure at rest (normal values: 89.4–112.2 mm Hg).

As part of the follow-up protocol, patients underwent an assessment of pain syndrome as per a visual analogue scale (VAS) and an assessment of anal sphincter insufficiency (ASI) as per Wexner's scale by completing a questionnaire before and daily after surgery.

If a anal fistula was suspected, patients underwent transrectal ultrasound of the anal canal.

Methods of Treatment and Management of Patients in the Postoperative Period

The patients were placed in a supine position with their knees bent as much as possible and their legs brought to their stomachs. In the control group, the anodermic defect was first excised in accordance with clinical guidelines using a double-leaf mirror [1], after which botulinum toxin type A (without complexing proteins) was injected into the internal anal sphincter. The agent was injected into four anatomical points (1, 5, 7, 11 o'clock of the conventional clock) with 20 units each (a total of 80 units) using an insulin syringe per 100 units. Patients in the main group were exclusively injected with botulinum toxin type A at the same points of the sphincter at a dosage of 80 units.

All patients in the postoperative period, within 60 days, were prescribed local dioxomethyltetrahydropyrimidine ointment therapy aimed at wound healing. Pain relief was carried out with the help of local or systemic medications in an individual regimen, depending on the degree of its intensity. Patients with impaired bowel movements at the stage of preparation for surgery and in the postoperative period were recommended to adjust nutrition, including a sufficient amount of fluid and dietary fiber, to optimize the motor

Table 1. *Baseline characteristics of patients*

Indicators	BTA 80 UN N = 65	BTA 80UN + FE N = 61
Age, years	37 (30; 46)	37 (31; 45)
Gender		
Male	22 (33.8%)	20 (32.8%)
Female	43 (66.2%)	41 (67.2%)
BMI, kg/m^2	23.9 (21.0; 29.4)	23.2 (21.2; 26.5)
Number of childbirths in history		
1	16/43 (37.2%)	12/41 (29.3%)
2	8/43 (18.6%)	11/41 (26.8%)
3	1/43 (2.3%)	3/41 (7.3%)
Complicated childbirths in history	2/25 (8.0%)	5/26 (19.2%)
History of the disease, months	24 (6; 36)	36 (15; 60)
Anal fissure		
1	57 (87.7%)	48 (78.7%)
2	8 (12.3%)	13 (21.3%)
Localization of anal fissure		
Posterior fissure (localization at 6 o'clock)	44 (67.7%)	39 (63.9%)
Anterior fissure (localization at 12 o'clock)	13 (20.0%)	9 (14.8%)
Posterior and anterior fissures (localization at 6 and 12 o'clock)	8 (12.3%)	13 (21.3%)
External hemorrhoidal node		
1	1 (1.5%)	2 (3.3%)
2	1 (1.5%)	2 (3.3%)
3	2 (3.1%)	6 (9.8%)
Internal hemorrhoidal node		
1	0	1 (1.6%)
2	0	1 (1.6%)
3	1 (1.5%)	6 (9.8%)
Hypertrophied anal papilla		
1	3 (4.6%)	4 (6.6%)
2	0	2 (3.3%)
Sentinel skin tag		
1	11 (16.9%)	18 (29.5%)
2	1 (1.5%)	1 (1.6%)

evacuation function of the gastrointestinal tract in order to form a regular shaped stool in the patient. In cases of ineffectiveness of a diet therapy, osmotic laxatives were prescribed with monitoring of their effectiveness [1].

The primary point of the study:

- Epithelialization of the defect / postoperative wound on the 60th day after surgery.

Secondary points of the study:

- Epithelialization of the defect / postoperative wound on days 15, 30, and 45 after surgery.
- Incidence and structure of postoperative complications.
- The intensity of pain during the day and during bowel movements for 60 days after the treatment.
- The incidence of IAS spasm on days 30 and 60 after the treatment.
- The disability (days).
- Factors presumably influencing the non-healing of the defect/ postoperative wound on days 30, 45 and 60.
- Factors presumably influencing the presence of ASI on days 30 and 60.

The hypothesis of the study is that the use of botulinum toxin type A in combination with fissure excision is superior to the isolated use of BTA in the epithelialization of a postoperative wound on day 60.

Calculation of the sample size: with the expected rate of defect epithelialization at 66.7% [7] with isolated use of BTA and for a postoperative wound, when this technique is supplemented with fissure

excision, it is 86% [2] on day 60, 146 patients need to be recruited in order to obtain a statistically significant difference with an 80% probability of a 5% type I error. With an expected patient dropout of 15%, the required number of patients for randomization was increased to 167. The initial characteristics of the included patients in the study are presented in Table 1.

All the patients included (65 in the BTA group and 61 in the BTA + FE) underwent a follow-up, profilometry, assessment of pain intensity and transient ASI. On day 15, all the included patients also showed up for a follow-up and filled out questionnaires to assess the intensity of pain, but the attendance at the remaining control points was not one hundred percent. In order not to lose data on those patients, they were not excluded from the analysis. Thus, the number of patients in each group who underwent one or another method of examination at 5 control points is shown in Fig. 2.

Statistical Analysis

The data analyzed in the study was entered into an Access relational database (Microsoft Office 2013). The statistical data analysis was performed in RStudio (Rv. 4.4.1 (RCoreTeam, Vienna, Austria)) using the libraries RODBC, dplyr, gtsummary, ggplot2, GenBinomApps. Qualitative values are given as absolute and relative incidences (*n* (%) or *n*/N (%)); quantitative and qualitative ordinal signs (with the number of possible values > 5) are given as medians, lower and upper quartiles (Me (Q1; Q3)). For the primary point of the study (the dichotomous value), a 95% coincidence interval (CI) was calculated using Clopper-Pearson's method. The groups were compared by qualitative values of Pearson's c^2-test with expected values of over 10 for four-field tables and over 5, for at least 20% of cases for multi-field tables; in the other cases, the two-way precise Fisher's test was used. When comparing the groups by quantitative and qualitative ordinal values (with the number of possible values > 5), Wilcoxon's rank test was used; Wilcoxon's continuity-adjusted test was used to evaluate the differences between two cases time-points within the same group. The search for factors that could be associated with the outcome was carried out using a univariate logistic regression analysis indicating the value of the odds ratio (OR) and its 95% CI using Wald's method. The differences were considered statistically significant at $p < 0.05$. To visualize the results, span diagrams and a histogram with grouping were also built.

RESULTS

Despite the comparable rate of epithelialization on day 60: 46/59 (78.0%; 95% CI: 65.2–87.7) in the main group versus 34/50 (68.0%; 95% CI: 53.3–80.5) in the control group ($p = 0.3$), at earlier control points, a statistically significantly higher rate of epithelialization was observed in patients in the group without fissure excision. So, on day 15, the defect healed in 12/65 (18.4%) patients in the isolated BTA group, whereas in the BTA + FE group, the postoperative wound did not heal in

Examination methods	Before surgery day	15 day	30 day	45 day	60 day
Follow-up examination	BTA N = 65 BTA + FE N = 61	BTA N = 65 BTA + FE N = 61	BTA N = 55 BTA + FE N = 53	BTA N = 51 BTA + FE N = 52	BTA N = 53 BTA + FE N = 50
Assessment of pain intensity	BTA N = 65 BTA + FE N = 61	BTA N = 65 BTA + FE N = 61	BTA N = 53 BTA + FE N = 52	BTA N = 51 BTA + FE N = 52	BTA N = 50 BTA + FE N = 50
Profilometry	BTA N = 65 BTA + FE N = 61	was not carried out	BTA N = 56 BTA + FE N = 52	was not carried out	BTA N = 52 BTA + FE N = 50
Assessment of transient ASI	BTA N = 65 BTA + FE N = 61	was not carried out	BTA N = 60 BTA + FE N = 53	was not carried out	BTA N = 52 BTA + FE N = 50

Figure 2. *The number of patients in the main and control groups who underwent examinations (follow-up, assessment of pain intensity, profilometry, assessment of transient anal sphincter incontinence) before surgery, on the 15th, 30th, 45th and 60th days after it*

anyone, $p = 0.0003$; on day 30, in 18/59 (30.5%) versus 1/53 (1.9%), $p < 0.0001$; on day 45 — it was 31/57 (54.4%) versus 3/52 (5.8%), $p < 0.0001$ (Fig. 3).

Thus, the rate of non-healing defect (the main group) was 13/59 (22.0%) cases, and the rate of postoperative wounds (the control group) was 16/50 (32.0%), $p = 0.3$ (Fig. 4).

Five patients in the BTA group and three in the BTA + FE group with non-healing wounds developed intra-sphincter rectal fistulas, confirmed by ultrasound of the anal canal. All fistulas were excised on a probe into the rectal lumen and healed within 60 days after the surgery. On the 60th day after the surgery, all the other patients with non-healing wounds were prescribed local therapies with a drug containing dexpanthenol to stimulate tissue healing. On the background of the therapy, the defect healed in two patients on the 75th and 90th days after surgery in the main group; in the control group, the postoperative wound epithelized in five patients on day 75 and in three patients — on day 90. In one patient with diagnosed intrarectal intussusception, the defect healed 6 months after isolated use of BTA. In the BTA + FE group, there was also a patient with a similar diagnosis, who had been diagnosed with a defect for more than a year. The patient refuses further surgery due to the absence of pain syndrome and phenomena of anal incontinence.

Additional procedures in the BTA group were performed to the following extent:

- Two patients underwent lateral internal (subcutaneous) sphincterotomy (LIS) without excision of the fissure; healing was achieved on day 60;
- One patient underwent fissure excision + BTA 40 units + platelet-enriched plasma (PRP). Healing was observed on day 45;
- One patient underwent fissure excision with drug relaxation with IAS-BTA 40units.

Subsequently, the patient's spasm was not detected, but the defect persisted; *E.Faecium* and *E.faecalis* were detected by polymerase chain reaction (PCR), which required the prescribing of antibacterial therapy, taking into account the sensitivity of the pathogen, for 2 weeks; on day 75, the wound in that patient healed;

- One patient underwent cicatricialt issue excision without an IAS spasm, and the healing was achieved within 60 days.

Additional surgeries in the BTA + FE group:

- One patient underwent LIS without fissure excision; the healing was achieved on day 60;
- One patient, due to the ineffectiveness of the therapy and the absence of IAS spasm, the cicatricial tissues in the area of the defect were excised and a swab from the wound was taken to detect sexually transmitted diseases, as well as to identify the bacterial flora. *P.mirabilis, P.vulgaris*, and *E.Faecium* were detected, which required the administration of antibacterial therapy, taking into account the sensitivity of the pathogen; within two months, the wound in that patient healed;
- One patient, without IAS spasm, underwent cicatricial tissue excision + PRP; the healing was achieved on day 45;

One patient did not appear for further control and treatment.

The incidence of postoperative complications was comparable in both groups — in the main group in

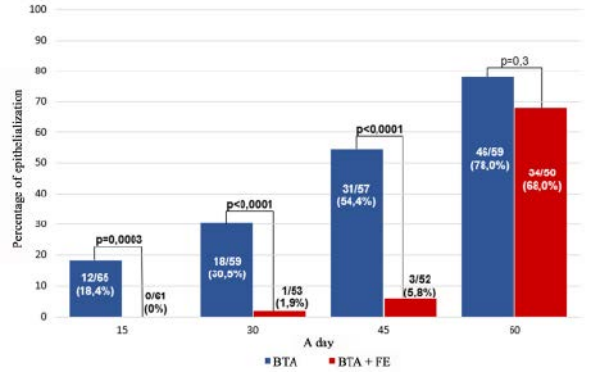

Figure 3. *Frequency of epithelialization of the defect (main group) and postoperative wound (control group) on days 15, 30, 45 and 60 among the patients*

NOTE: If the patient initially had two CAFs, the healing of both defects/postoperative wounds was considered the fact of epithelialization. If the patient did not come for follow-up, but there was a previously established epithelialization of the defect/ postoperative wound, then such a patient was counted in the healing group up to and including 60 days

Table 2. *Frequency and structure of postoperative complications*

Indicators	BTA	BTA + FE	p-value
Rate of postoperative complications	23/65 (35.4%)	23/61 (37.7%)	0.8
Transient ASI on day 30 after surgery	15/60 (25.0%)	18/53 (34.0%)	0.3
Transient ASI on day 60 after surgery	7/60 (11.7%)	9/51 (17.6%)	0.4
Thrombosis of external hemorrhoidal nodes	2/65 (3.1%)	2/61 (3.3%)	1.0
Intrasphincteric fistula	5/60 (8.3%)	3/50 (6.0%)	0.7

23/65 (35.4%) patients and in 23/61 (37.7%) patients in the control group, $p = 0.8$. Transient ASI on day 30 was observed in 15/60 (25.0%) patients with isolated use of BTA and in 18/53 (34.0%) patients with combination its administration with FE, $p = 0.3$; on day 60 — in 7/60 (11.7%) and 9/51 (17.6%), respectively, $p = 0.4$. Thrombosis of external hemorrhoidal nodes developed in 2/65 (3.1%) patients of the main group and in 2/61 (3.3%) patients of the control group, $p = 1.0$; intra-sphincter fistula in 5/60 (8.3%) and 3/50 (6.0%) patients, respectively, $p = 0.7$ (Table 2).

After surgery, there was a decrease in the intensity of pain in the main group, while in the control group the median and upper quartile exceeded the preoperative values up to the 3rd day, then these indicators returned to the preoperative level, where they remained up to the 8th day, after which they began to decrease. So, on day 7, patients assessed the severity of pain by 1 (0; 2) point in the main group versus 3 (2; 4) points in the control group ($p < 0.0001$); by 15 — 1 (0; 1) versus 1 (0; 2) points ($p = 0.0044$); by 30 — 0 (0; 0) versus 1 (0; 2) points ($p = 0.0024$); by 45 — 0 (0; 0) versus 0 (0; 1) points ($p = 0.023$); on day 48, the groups became comparable ($p = 0.22$); by day 60, almost all patients in both groups managed to relieve pain during the day ($p = 0.6$) (Fig. 5).

A similar pattern was found during defecation (Fig. 6). With the isolated use of BTA, the median score decreased immediately after surgery, whereas with the combination of this method with fissure excision, the values increased slightly on the 1–2 days after surgery, after which they returned to preoperative values and remained at this level up to the 6th day inclusive, after which the intensity of pain during bowel movements began to decrease. So, on day 7, it was 2 (1; 4) points in the main group and 5 (4; 6) points in the control group ($p < 0.0001$); on day 15, it was 1 (0; 3) versus 3

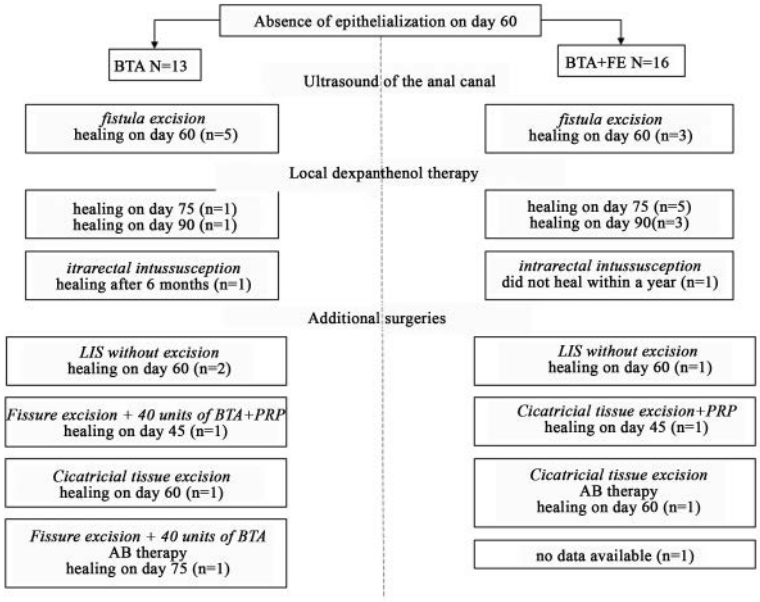

Figure 4. *Treatment methods for patients with long-term non-healing wounds*

(2; 4) points ($p < 0.0001$); by day 30 — 0.5 (0; 1) versus 2 (1; 3) points ($p = 0.0002$); by day 45 — 0 (0; 1) versus 1 (0; 2) points ($p = 0.0028$); by day 49, comparability of groups was achieved — 0 (0; 1) versus 0 (0; 1) points ($p = 0.15$); on day 60, the median and upper quartile remained unchanged in the both groups ($p = 0.8$).

Before surgery, the maximal pressure in the anal canal at rest was 129 (121; 139) mm Hg in the main group and 126 (118; 135) mm Hg in the control group ($p = 0.18$). On day 30, both groups showed a significant decrease in the values of the indicator compared to the baseline data (both $p < 0.0001$): up to 105 (83; 124) mm Hg in the BTA group and 85 (72; 144) mm Hg in the BTA + FE group ($p = 0.012$). On day 60, there was a continued decrease in the maximal pressure in the anal canal at rest in both groups, but it was not significant compared to the previous control point ($p = 0.3$ for the main group and $p = 0.056$ for the control group), but the differences between the groups were significant: 96 (83; 118) mm Hg versus 77 (69; 90) mm Hg ($p = 0.0001$), respectively (Fig. 7).

The mean pressure in the anal canal at rest before surgery was 65 (62; 67) mm Hg in the main group and 64 (62; 67) mm Hg in the control group ($p = 0.6$). On day 30, both groups showed a significant decrease in the values of the indicator (both $p < 0.0001$): 50 (42; 63) mm Hg for isolated use of BTA versus 43 (38; 49) mm Hg in its combination with FE ($p = 0.0004$); on day 60, the values remained approximately at the same level ($p = 0.7$ for the main group and $p = 0.9$ for the control group) and amounted to 54 (46; 63) mm Hg versus 42 (37; 49) mm Hg ($p = 0.0001$), respectively (Fig. 8).

According to profilometry, IAS spasm persisted in 22/56 (39.3%) patients of the main group and 16/52 (30.8%) patients of the control group ($p = 0.4$); on day 60 — in 22/52 (42.3%) and 8/50 (16.0%) patients ($p = 0.004$), respectively (Table 3).

At the same time, in patients of the main group, despite the healed anodermic defect, IAS spasm persisted in 14/38 (36.8%) patients, whereas in the control group, a similar picture with a postoperative wound was observed in 3/34 (8.8%) patients ($p = 0.006$). In the absence of epithelialization, not all patients retained spasm: in the BTA group — 8/14 (57.1%) patients, in the BTA + FE group — 5/16 (31.3%) patients ($p = 0.3$) (Table 4).

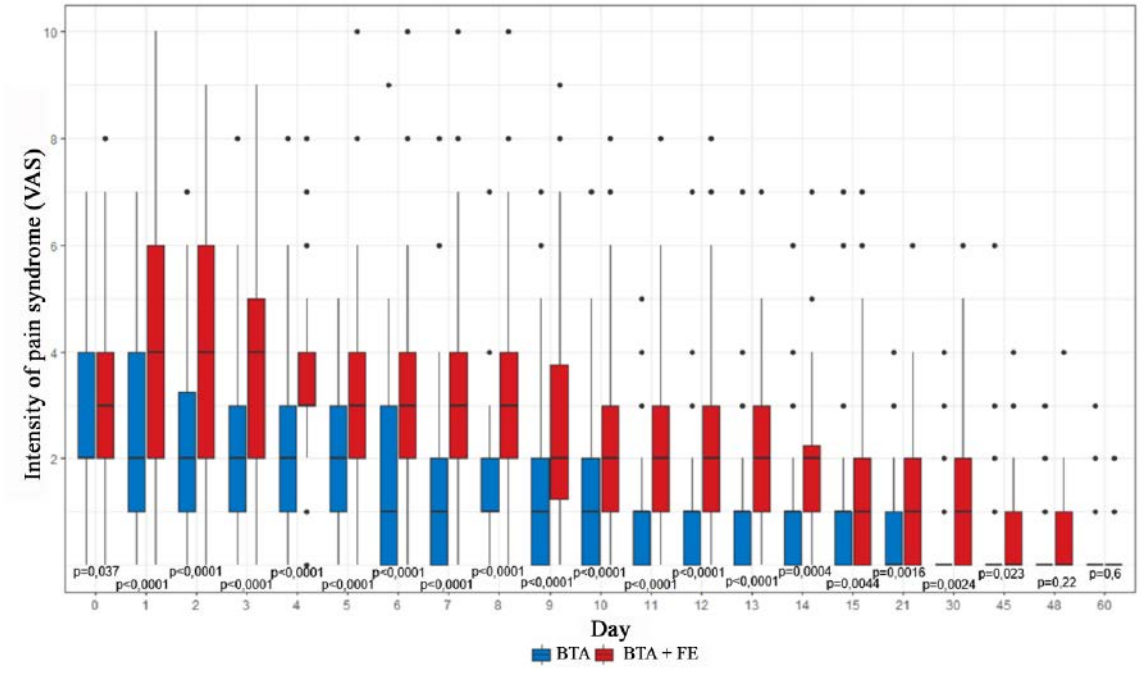

Figure 5. *Box plot illustrating the intensity of pain syndrome (according to the VAS) during the day in main and control groups*

Table 3. *Presence of spasm of internal anal sphincter on days 30 and 60 after surgery in the main and control groups*

Indicator	Day 30 after surgery			Day 60 after surgery		
	BTA N = 56	BTA + FE N = 52	p-value	BTA N = 52	BTA + FE N = 50	p-value
IAS spasm	22 (39.3%)	16 (30.8%)	0.4	22 (42.3%)	8 (16.0%)	0.004

Table 4. *Comparison of the fact of healing of the defect / postoperative wound and the presence of spasm of internal anal sphincter on the 60th day after surgery in the main and control groups*

Indicator	Healing of the defect / postoperative wound on day 60					
	Yes			No		
	BTA N = 38	BTA + FE N = 34	p-value	BTA N = 14	BTA + FE N = 16	p-value
IAS spasm	14 (36.8%)	3 (8.8%)	0.006	8 (57.1%)	5 (31.3%)	0.3

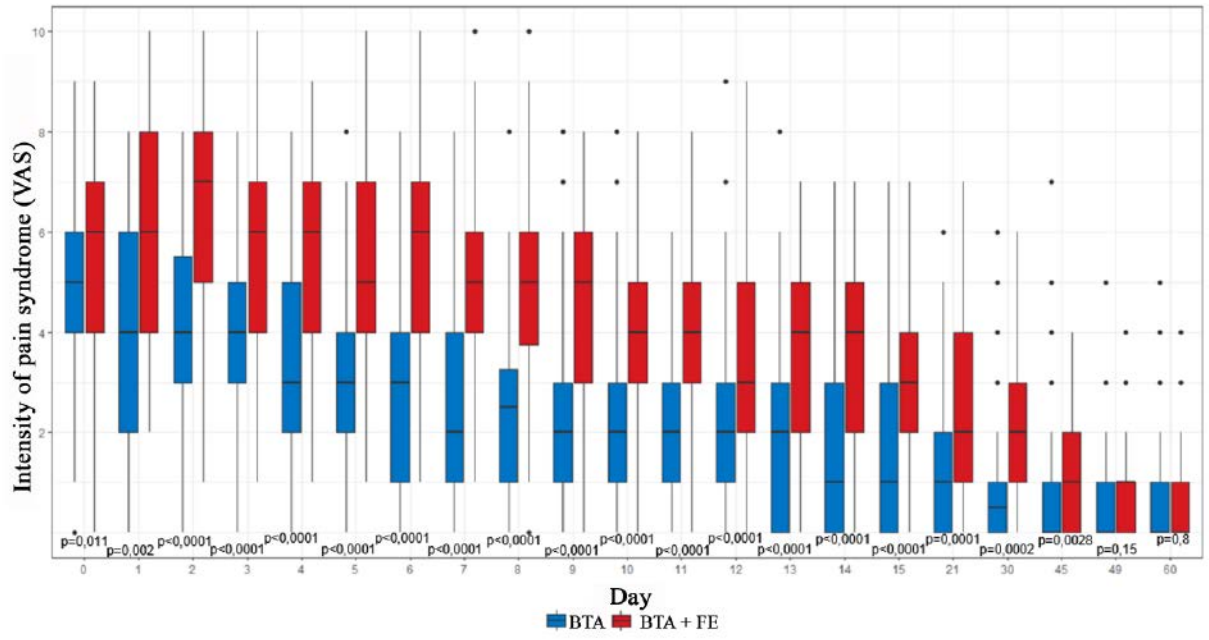

Figure 6. *Box plot illustrating the intensity of pain syndrome (according to the VAS) during the defecation in main and control groups*

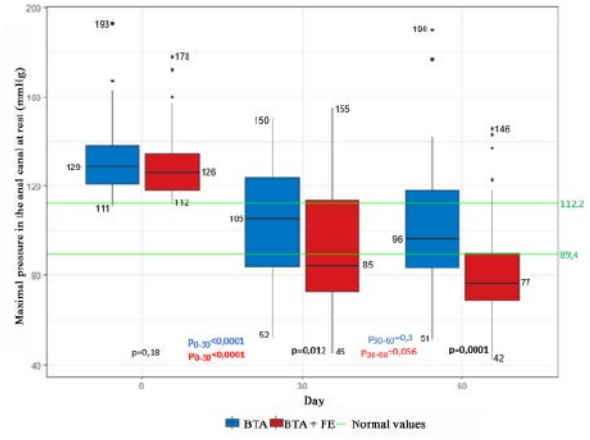

Figure 7. *Box plot illustrating the maximum pressure in the anal canal at rest in the main and control groups according to profilometry results*

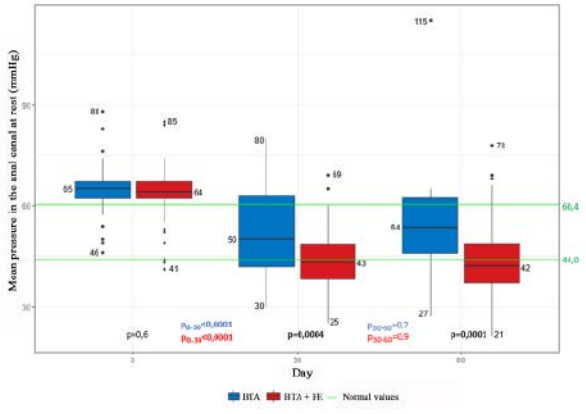

Figure 8. *Box plot illustrating the mean pressure in the anal canal at rest in the main and control groups according to profilometry results*

Table 5. *Factors presumably influencing the non-healing of the defect / postoperative wound on days 30, 45, and 60 after surgery*

Indicators	Day 30		Day 45		Day 60	
	OR (95% CI)	p-value	OR (95% CI)	p-value	OR (95% CI)	p-value
The method of treatment BTA BTA + FE	 1 22.8 (2.93–178.0)	0.003	 1 19.5 (5.43–69.8)	< 0.0001	 1 1.67 (0.71–3.92)	0.2
Gender Male Female	 1 2.32 (0.85–6.35)	0.102	 1 2.33 (0.99–5.47)	0.053	 1 1.01 (0.40–2.53)	1.0
Age, years	0.99 (0.95–1.03)	0.6	0.99 (0.96–1.03)	0.7	1.00 (0.97–1.04)	0.8
Anamnesis, months	1.00 (0.99–1.01)	0.6	1.00 (1.00–1.01)	0.3	1.00 (0.99–1.01)	0.6
BMI, kg/m^2	0.99 (0.90–1.09)	0.8	0.98 (0.91–1.06)	0.6	1.04 (0.95–1.12)	0.4
IAS spasm	0.80 (0.26–2.45)	0.7	–	–	2.68 (1.08–6.66)	0.034
CAF localization Anterior Posterior	 1 0.34 (0.09–1.23)	0.099	 1 0.81 (0.36–1.86)	0.6	 1 1.11 (0.47–2.63)	0.8
Sentinel skin tag	1.16 (0.35–3.87)	0.8	1.31 (0.49–3.49)	0.6	0.63 (0.21–1.86)	0.4

In the group with isolated use of BTA, the days of disability were significantly fewer than in the group with a combination of BTA with FE — 7 (6; 15) versus 20 (15; 30) days ($p < 0.0001$) (Fig. 9).

Significant factors increasing the chances of absence of epithelialization on day 30 were the treatment of BTA + FE (OR = 22.8; 95% CI: 2.93–178.0; $p = 0.003$), as well as on day 45 (OR = 19.5; 95% CI: 5.43–69.8; $p < 0.0001$). At the same time, on day 60, only the presence of IAS spasm was significantly associated with non-healing (OR = 2.68; 95% CI: 1.08–6.66; $p = 0.034$). No statistically significant association with non–healing was found for the other signs we considered: gender, age, duration of medical history, body mass index, location of CAF, and the presence of sentinel skin tag (Table 5). The remaining formations of the anal canal were not taken into account in the analysis due to their small number.

When assessing the factors that could affect the presence of ASI on days 30 and 60 after surgery, neither the treatment method, nor gender, nor age, nor the time of medical history, nor BMI, nor the number of childbirths in history, nor complicated childbirths were associated with the risk of anal incontinence (Table 6).

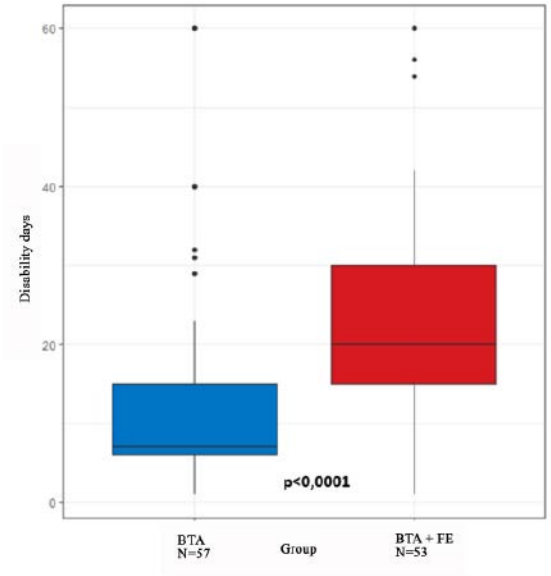

Figure 9. *Box plot illustrating disability days in main and control groups*

DISCUSSION

The effectiveness of botulinum toxin in the treatment of CAF varies from 19% to 100% [8]. Such a wide range is due to differences in the doses of the drug, injection methods, as well as the lack of consensus on the standard healing time for a chronic anodermic defect after surgery. According to a systematic review of the literature by Boland et al. [7] in 2020, included in the calculation of the sample size, the healing rate in the BTA group was 66.7%for 8 weeks.

Also, according to a recent meta-analysis conducted by Thippeswamy et al. in 2025[8], the use of botulinum toxin demonstrated defect healing in

Table 6. *Factors presumably influencing the presence of ASI on days 30 and 60 after surgery*

Indicators	Day 30		Day 60	
	OR (95% CI)	p-value	OR (95% CI)	p-value
The method of treatment		0.3		0.4
BTA	1		1	
BTA + FE	1.54 (0.68–3.49)		1.62 (0.56–4.72)	
Gender		0.3		1.0
Male	1		1	
Female	1.59 (0.63–4.00)		1.02 (0.32–3.18)	
Age, years	0.99 (0.95–1.02)	0.4	1.01 (0.96–1.05)	0.8
History, months	1.00 (0.99–1.01)	1.0	1.00 (0.99–1.01)	0.8
BMI, kg/m^2	0.94 (0.86–1.03)	0.2	1.06 (0.96–1.17)	0.3
Number of childbirths*				–
0	1	–	1	0.3
1	0.69 (0.23–2.10)	0.5	0.37 (0.06–2.09)	0.7
2	0.58 (0.16–2.07)	0.4	1.31 (0.30–5.73)	1.0
3	0.82 (0.07–10.1)	0.9	0.00 (0.00–µ)	
Complicated childbirths**	0.37 (0.02–2.49)	0.4	1.48 (0.14–15.4)	0.7

*Note: *The calculation was carried out among women; ** The calculation was carried out among women who had given birth*

1,117/1,532 (72.7%; 95% CI: 67.3–78.1; $p < 0.001$) patients after the first injection for 6–12 months. When analyzing our data, despite the hypothesis put forward, the rate of epithelialization of the anodermic defect/postoperative wound on day 60 was 46/59 (78.0%; 95% CI: 65.2–87.7) with isolated use of BTA versus 34/50 (68.0%; 95% CI: 53.3–80.5) with its combination with excision of the anodermic defect ($p = 0.3$). At the same time, the results obtained on the effectiveness of the isolated use of BTA are consistent with the current data from the world literature.

According to the results of the study, with a comparable rate of epithelialization of the anodermic defect and the postoperative wound on day 60, the healing rates of the anal fissure on days 15, 30, and 45 were significantly higher. This is probably due to the size of the wound defect, which significantly exceeds the initial size of the anal fissure in area, since the presence of a postoperative wound in the anal canal was the only predictor responsible for reducing the rate of epithelialization on days 30 and 45 of the postoperative period. This is confirmed by the data by Hryukin R.Yu. et al., which showed that the risk of non-healing of a postoperative wound increased significantly with an increase in the surgery volume [2].

Similar results were obtained when comparing isolated LIS and its combination with fissure excision [6], where the use of LIS alone made it possible to shorten the epithelialization time and reduce the intensity of pain. At the same time, as in this study, the only factor affecting the rate of epithelialization on days 30 and 45 was the combined treatment method. No factors affecting epithelialization on day 60 were identified. At the same time, in our study, the chance of non-healing on day 60 was statistically significantly associated with persistent IAS spasm. This indicates its significant role in the pathogenesis of chronic anal fissure. At the same time, in some patients with epithelized wounds, IAS spasm was not eliminated: 14/38 (36.8%) patients in the main group and 3/34 (8.8%) patients in the control group. Apparently, this indicates the presence of additional pathogenetic factors that hinder or promote full-fledged repair. This case justifies the need to introduce an expanded diagnostic algorithm, including an assessment of the microbiome, the functional state of the rectal sphincter, as well as studying the interaction between structural changes in the sphincter, chronic inflammation and neurogenic disorders.

As in the case of isolated use of LIS [6], administration of botulinum toxin alone without excision of the anal fissure significantly reduced the intensity of postoperative pain for the entire follow-up period. These data confirm the concept that the

leading mechanism of pain after anal canal surgery is inflammation in the surgical area [9,10].

Avoiding of fissure excision, by acceleration of epithelialization and reducing the intensity of pain, significantly reduced the number of days of temporary disability in the group of isolated use of BTA. Corresponding results were obtained in the case of lateral internal (subcutaneous) sphincterotomy without fissure excision.

When assessing the functional state of the internal anal sphincter, both methods showed a significant decrease in both maximal and mean pressure in the anal canal at rest for the entire follow-up. At the same time, on days 30 and 60 in the group with fissure excision, the values of these indicators were significantly lower. According to some authors, including a randomized study conducted by Bara B.K. et al. [12], excision of the anal fissure, even as an independent treatment method, is accompanied by a significantly higher incidence of postoperative complications, including anal sphincter insufficiency, than after isolated LIS [11–13]. It is worth noting that this did not affect the incidence of transient ASI in our study, and the changes of these indicators steadily improved in both groups for the entire follow-up. No factors that could influence transient anal sphincter insufficiency were identified.

These changes are most likely due to sphincter divulsion with a double-leaf mirror during excision of the defect, the presence of a wound in the anal canal, and severe pain in the postoperative period. Considering the above, just as in the case of lateral internal (subcutaneous) sphincterotomy, most authors suggest using BTA as monotherapy, and resorting to fissure excision only if there is no effectiveness for at least 8 weeks after isolated use of botulinum toxin [14]. According to Lindsey et al. (2004), excision of the anodermic defect is justified only in chronic fissures resistant to drug treatment, including botulinum toxin, and in no case, should it be considered as routine practice [15].

CONCLUSION

Avoiding fissure excision when using BTA at a dosage of 80 units makes it possible to achieve epithelialization of the defect in the early postoperative period; to achieve a lower intensity of pain syndrome and significantly reduce the number of days of temporary disability.

AUTHORS CONTRIBUTION

Concept and design of the study: *Evgeny E. Zharkov, Karina I. Sagidova, Aleksey A. Ponomarenko*

Collection and processing of the material: *Karina I. Sagidova, Evgeny E. Zharkov, Ekaterina Yu. Lebedeva, Maria A. Ignatenko*

Text writing: *Karina I. Sagidova, Maria A. Ignatenko*

Statistical processing: *Maria A. Ignatenko, Karina I. Sagidova*

Editing: *Evgeny E. Zharkov, Aleksey A. Ponomarenko, Andrey A. Mudrov, Ivan V. Kostarev*

INFORMATION ABOUT THE AUTHORS (ORCID)

Karina I. Sagidova — 0000-0001-7373-9103

Maria A. Ignatenko — 0009-0005-1182-419X

Evgeny E. Zharkov — 0000-0003-3403-9731

Aleksey A. Ponomarenko — 0000-0001-7203-1859

Ekaterina Yu. Lebedeva — 0000-0002-3590-112X

Ivan V. Kostarev — 0000-0002-1778-0571

Andrey A. Mudrov — 0000-0002-1207-5988

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