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Treatment of chronic anal fissure botulinum toxin type A 40 U in comparison with lateral subcutaneous sphincterotomy (NCT03855046)

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ABSTRACT *AIM: to improve the results of chronic anal fissure treatment.*
PATIENTS AND METHODS: the prospective randomized study included 176 patients divided in two groups. Eighty-eight patients underwent fissure excision in combination with injection of botulinum toxin type A (incobotulinum toxin) into the internal anal sphincter (main group, BTA), and 88 patients underwent anal fissure excision in combination with lateral subcutaneous sphincterotomy (control group, LIS).
RESULTS: on the 30th day after surgery, spasm of internal anal sphincter, according to profilometry, persisted in 14.8% of patients of the main group (BTA) and 22.7% of patients in the control group (LSS) (p = 0.18), and on the 60th day in 20.4% and 14.8% of patients, respectively (p = 0.32). On the 60th day after surgery, the postoperative wound did not epithelialize in 14% of patients in the BTA group and 1% of the LSS group (p = 0.0006). On the 30th day after surgery, complaints of incontinence were noted by 32% of patients in the BTA group and 31% in the LSS group (p = 0.87), on the 60th day — 7% and 11% of patients, respectively (p = 0.29). The intensity of pain after surgery in the compared groups did not differ both after defecation and during the day (p > 0.05). Expansion of the surgery volume increases the chance of developing temporary anal sphincter incontinence (ASI) by 2.44 times on the 30th day of observation (p = 0.01) and by 3 times — on day 60 (p = 0.04). The use of BTA as a method of internal anal sphincter relaxation increases the chance of slowing down the epithelization of the postoperative wound by 13.7 times [p = 0.01], and the expansion of the surgery volume — by 3.47 times [p = 0.03].
CONCLUSION: the use 40 U of botulinum toxin type A after anal fissure excision is not inferior to lateral subcutaneous sphincterotomy in elimination of spasm internal anal sphincter with a comparable incidence of temporary anal sphincter incontinence within 2 months after surgery. Neurotoxin serves as an alternative to sphincterotomy, however, in some cases, it requires the addition of a agent containing human recombinant epidermal growth factor to the postoperative management of patients.

KEYWORDS: *chronic anal fissure, CAF, internal sphincter spasm, botulinum toxin type A, BTA, incobotulinum toxin, lateral subcutaneous sphincterotomy, LIS.*

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INTRODUCTION

Currently, the main method of treatment of chronic anal fissure (CAF) is lateral subcutaneous sphincterotomy (LSS) [1,2]. However, LSS is accompanied by the postoperative anal sphincter incontinence (ASI); and therefore the search continues for methods of the internal anal sphincter relaxation that do not lead to the development of ASI and, at the same time, are not inferior to sphincterotomy in the incidence

of fissure healing [3,4]. One of the proposed methods of treatment of chronic anal fissure is the injection of botulinum toxin type A into the internal anal sphincter (incobotulinum toxin, BTA). A meta-analysis of seven randomized clinical trials (RCTs) comparing LSS and BTA in the treatment of CAF showed that in the period of observation of patients from 4.5 to 60 months, the risk of temporary postoperative ASI after injection of neurotoxin into the internal anal sphincter is 0.86 times lower than after sphincterotomy, but BTA is inferior to LSS in the effectiveness of treatment of chronic anal fissure. Despite the meta-analysis of RCTs, they used various methods of injection of the drug without excision of the fissure, which may affect the effectiveness of treatment of patients with CAF [5]. We proposed a method for the treatment of chronic anal fissures, consisting in excision of the fissure with injection of BTA into the internal anal sphincter at a dosage of 40 units, leading to epithelization of the postoperative wound in all patients for 2 months with a minimum incidence of reversible anal sphincter incontinence. Thus, we decided to conduct a randomized study comparing the fissure excision in combination with LSS and the fissure excision in combination with the injection of botulinum toxin type A into the internal anal sphincter according to the proposed method in order to assess the incidence of ASI development and healing of postoperative wounds.

AIM

The aim of the study was to improve the results of chronic anal fissure treatment.

PATIENTS AND METHODS

In the period from November 2019 to September 2021, a prospective, randomized, single-center study on the basis of our Center, registered on the website www.ClinicalTrials.gov (ID NCT03855046) was done.

The main group included 88 patients who underwent fissure excision in combination with drug relaxation of the internal anal sphincter with botulinum toxin type A (BTA).The control group included 88 patients who underwent fissure excision in combination with lateral subcutaneous sphincterotomy (LSS) (Fig.1). The diagnosis of "chronic anal fissure" was established in the presence of at least one of the following signs: the duration of the disease history over 2 months, scars of the defect margins, fibrous polyp of the anal canal at the proximal edge of the defect, sentinel pile at the distal edge of the defect; fibers of the internal sphincter at the bottom of the defect.

Inclusion Criteria

Patients with chronic anal fissure with confirmed spasm of the internal sphincter according to profilometry; age of patients over 18 years; informed consent of the patient to participate in the study.

Non-inclusion Criteria

Patients who previously had surgery on the anal canal and rectum (with the exception of minimally invasive methods); the presence of anal sphincter incontinence of the I-III grade (by Wexner scale — over 0 points); pectenosis; inflammatory bowel diseases; external and internal hemorrhoids stage IV; fistula-in-ano; severe

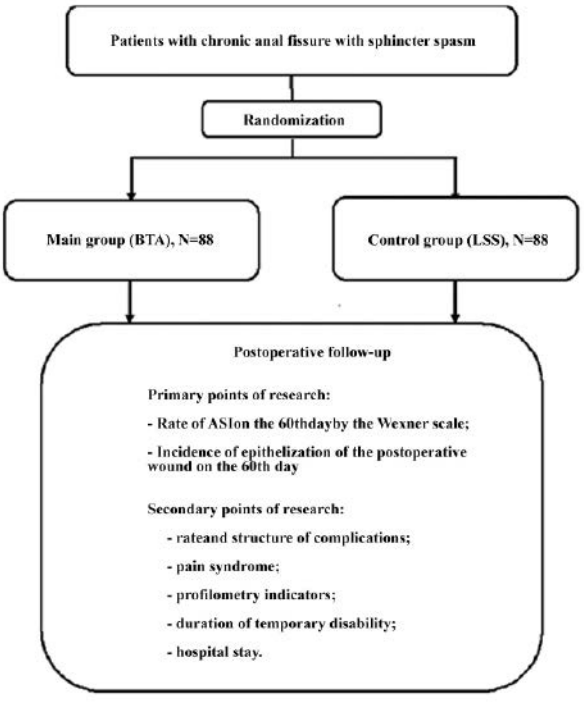

Figure 1. *Research design*

Table 1. *Clinical characteristics of patients with chronic anal fissure*

Indicator	Method of elimination of the internal sphincter spasm		*p*
	BTA, N = 88	LSS, N = 88	
Median age (quartiles)	37.5 (32; 45)	39 (33; 52)	0.08
Median BMI, kg/m^2 (quartiles)	24.3 (21.1; 28.3)	26.1 (22.2; 30.1)	0.07
Gender			
Male	34 (38.6%)	39 (44.3%)	0.54
Female	54 (61.4%)	49 (55.7%)	
History of the disease (months)	16.5 (6; 60)	18.5 (8.5; 50)	0.92
Median pain syndrome after stool (quartiles)	5 (4; 7)	6 (5; 8)	0.004
Median pain syndrome during the day (quartiles)	4 (3; 6)	5 (3; 6)	0.09
Anal fissure (N)			
1	74 (84%)	73 (82.9%)	0.84
2	14 (15.9%)	15 (17%)	
Internal fistula opening	4 (4.6%)	2 (2.3%)	0.4
Fibrous polyp (N)			
1	22 (25%)	33 (37.5%)	0.1
2	0	3 (3.4%)	0.7
Sentinel pile (N)			
1	22 (25%)	31 (35.2%)	0.18
2	3 (3.4%)	6 (6.8%)	0.5
External hemorrhoids (N)			
1	12 (13.6%)	6 (6.8%)	
2	4 (4.6%)	5 (5.7%)	0.41
3	5 (5.7%)	8 (9%)	
Internal hemorrhoids(N)			
1	7 (7.9%)	3 (3.4%)	0.14
2	1 (1.1%)	5 (5.7%)	
3	7 (7.9%)	4 (4.6%)	
Defecation			
Normal stool	23 (26.1%)	23 (26.1%)	1
Constipation	65 (73.9%)	65 (73.9%)	
Childbirth (N)	N = 54	N = 49	0.55
0	25 (46.3%)	18 (36.7%)	
1	11 (20.4%)	14 (28.6%)	
2	15 (27.8%)	16 (32.7%)	
3	2 (3.7%)	1 (2%)	
4	1 (1.8%)	0	
Complicated childbirth in history	11 (20.4%)	9 (18.4%)	0.8

comorbidities in the stage of decompensation; pregnancy and lactation, individual intolerance and hypersensitivity to botulinum toxin type A; myasthenia and myasthenic syndromes.

Exclusion Criteria

The presence of anal fistulas that capture the subcutaneous part of the external sphincter and deeper (during intraoperative revision); refusal to undergo examination, non-compliance with the study protocol.

All patients included in the study underwent profilometry before surgery, on the 30th and 60th days after surgery using Solar GI HRAM device (Netherlands). The presence of the internal anal sphincter spasm was established with an increase in at least one of the following profilometry indicators: mean pressure in the anal canal at rest (APACR), (norm: 44.0–60.4 mmHg), maximum pressure in the anal canal at rest (MPACR), (norm: 89.4–112.2 mmHg) [6]. Before surgery and day after it, patients assessed the pain syndrome on a visual-analog scale (VAS), answered questions on the Wexner incontinence scale. On the 7th, 30th and 60th days of follow-up, the

results of treatment were clinically evaluated: patients underwent a digital examination and anoscopy. Within two months after the surgery, an analysis of the intake of painkillers, the duration of temporary disability after surgery, as well as the duration of temporary anal incontinence, if present in the postoperative period, was performed.

Surgery was performed under spinal anesthesia in the position of the patient on his back with his legs as close to the abdomen as possible. Patients of the main group (BTA) after excision of the fissure according to the standard procedure [1] were injected with botulinum toxin type A, free of complexing proteins, into the internal anal sphincter at 1,5,7 and 11 o'clock at a dosage of 10 units of the drug (a total of 40 units) using an insulin syringe for 100 divisions. Patients of the control group (LSS) underwent fissure excision in combination with lateral subcutaneous sphincterotomy by closed or open method, depending on the preference of the surgeon [1].

If the patient had a fissure complicated by an incomplete internal fistula that did not capture parts of the external sphincter (intersphincteric fistula), the fistula fissure was excised in a single block within healthy tissues [1], in the presence of external and internal hemorrhoids of stage II-III, surgery was performed depending on the stage of this disease in accordance with clinical guidelines [7].

Patients of the main (BTA) and control (LSS) groups were homogeneous in age, body mass index (BMI), gender, and other clinical features (Table 1).

Patients of the main (BTA) and control (LSS) groups were also comparable in type of surgery aimed at eliminating the manifestations of hemorrhoidal disease (Table 2).

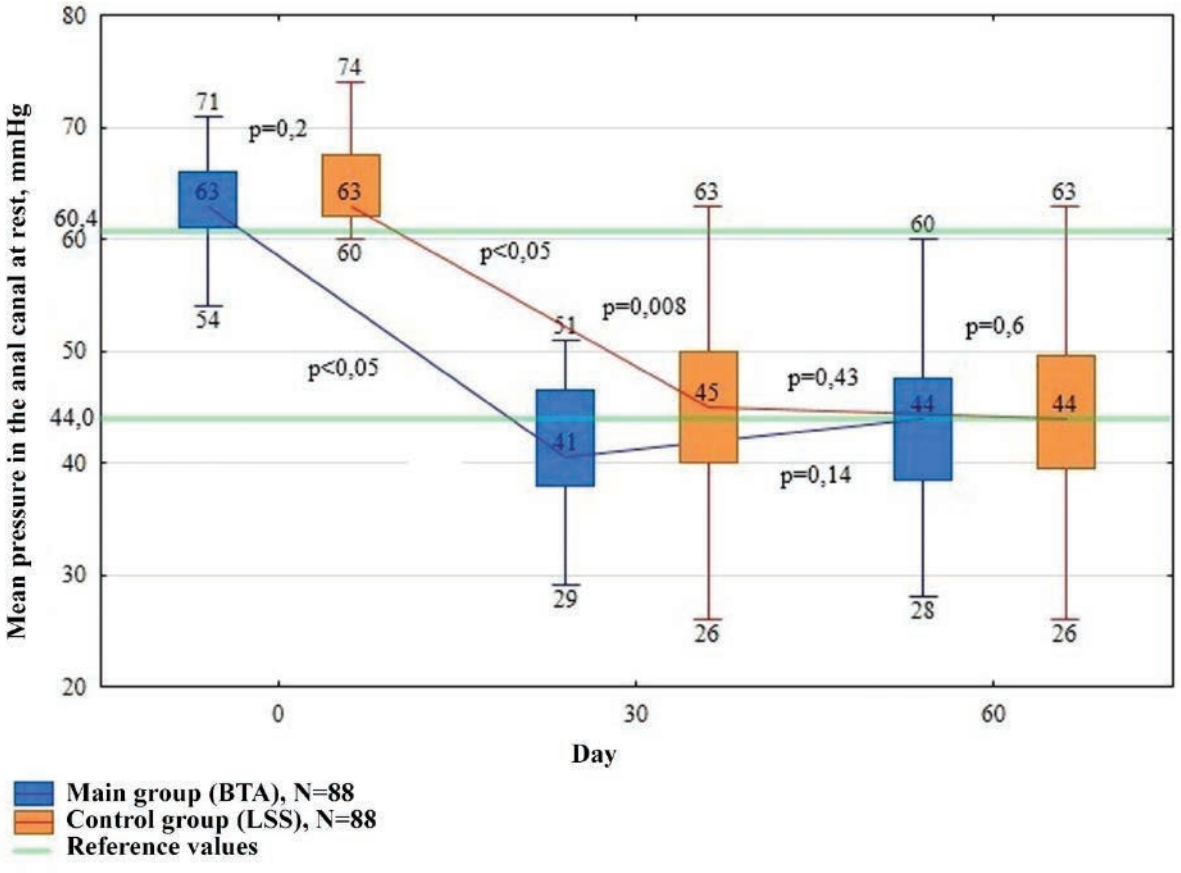

Figure 2. *Average pressure in the anal canal at rest before surgery and in the postoperative period*

Table 2. *Characteristics of patients operated for chronic anal fissure and concomitant hemorrhoidal disease*

Indicator	Method of elimination of the internal anal sphincter spasm		p
Form and stage of hemorrhoids	BTA, N = 88	LSS, N = 88	
External hemorrhoids	7 (7.9%)	8 (9%)	1
External and internal hemorrhoids of stage 2	4 (4.6%)	0	0.12
External and internal hemorrhoids of stage 3	7 (7.9%)	12 (13.6%)	0.34
Surgery volume for hemorrhoids			
Sclerosis of internal hemorrhoids, excision of external hemorrhoids	4 (4.6%)	0	0.12
Desarterization of internal hemorrhoids with mucopexia	0	1 (1.1%)	1
Desarterization of internal hemorrhoids with mucopexia, excision of external hemorrhoids	3 (3.4%)	4 (4.6%)	1
Excision of external hemorrhoids	7 (7.9%)	8 (9%)	1
Open hemorrhoidectomy	4 (4.6%)	7 (7.9%)	0.54

Table 3. *Spasm of the internal anal sphincter on days 30 and 60 after surgery*

The internal anal sphincter spasm	Day 30			Day 60		
	BTA, N = 88	LSS, N = 88	p	BTA, N = 88	LSS, N = 88	p
Yes	13 (14.8%)	20 (22.7%)	0.18	18 (20.4%)	13 (14.8%)	0.32
No	75 (85.2%)	68 (77.3%)		70 (79.6%)	75 (85.2%)	

Table 4. *Frequency and structure of postoperative complications*

Complications	Method of the internal anal sphincter relaxation		p
	Main Group (BTA), N = 88	Control Group (LSS), N = 88	
Hematoma	1 (1%)	22 (25%)	0.0001
Thrombosis of external hemorrhoids	4 (5%)	3 (3%)	0.7
Urinary retention	1 (1%)	1 (1%)	1
Bleeding in the early postoperative period	0	1 (1%)	0.24
Long-term non-healing wound	12 (14%)	1 (1%)	0.0006
Temporary ASI on the 30th day after surgery	28 (32%)	27 (31%)	0.87
Temporary ASI on the 60th day after surgery	6 (7%)	10 (11%)	0.29

RESULTS

On the 30th day of follow-up in the compared groups, a significant decrease in the mean pressure in the anal canal at rest was revealed compared with the parameters of profilometry before surgery [$p < 0.05$], while the APACR on the 30th day after surgery was lower in the BTA group [$p = 0.008$] (Fig.2).

Nevertheless, on the 30th day after surgery, spasm of the internal anal sphincter according to profilometry (APACR and MPACR indicators) persisted in 13/88 (14.8%) patients of the main group (BTA) and 20/88 (22.7%) patients of the control group (LSS) ($p = 0.18$). On the 60th day of follow-up, there was an increase in the number of patients with sphincter spasm in the BTA group to 18/88 (20.4%), and in the LSS group — a decrease to 13/88 (14.8%) ($p = 0.32$), (Table 3).

Within 60 days after surgery, the patients included in the study were evaluated for the incidence and nature of complications (Table 4).

Hematoma of the perianal area was detected in 1/88 (1%) patients of the BTA group and in 22/88 (25%) patients of the LSS group ($p = 0.0001$). The single hematoma in a patient after surgery in the main group (BTA) was associated with the open hemorrhoidectomy (external and internal hemorrhoids of stage III) and the need for them to take anticoagulants in connection with earlier surgery on the mitral valve. Hematomas in 22/88 (25%) patients of the control group (LSS) were associated with the technical features of

Table 5. *Factors associated with the development of transient AI on day 30 after surgery*

Factor	OR (CI 95%)	p
Method of internal sphincter relaxation		
BTA	1	
LSS	0.95 (0.5–1.79)	0.87
Surgery type		
Standard	1	
Extended	2.44 (1.22–4.87)	0.01
Age	1.03 (0.99–1.05)	0.07
BMI	0.99 (0.93–1.06)	0.78
Gender		
Male	1	
Female	1.71 (0.88–3.34)	0.11
Childbirth (N)		
0	1	
1	1.17 (0.41–3.28)	0.77
2	1.3 (0.5–3.43)	0.58
3 and more	2.07 (0.26–16.3)	0.49
Complicated childbirth		
No	1	
Yes	0.95 (0.34–2.64)	0.92

performing sphincterotomy: bleeding into the subcutaneous tissue of the perianal area after dissection of the internal sphincter. It is worth noting that this complication was not clinically significant and did not require additional prescriptions in any case.

Bleeding after surgery occurred in 1/88 (1%) patient of the control group (LSS), which required stitching of the vessel in the site of the postoperative wound ($p = 0.24$).

On the 60th day of follow-up, the postoperative wound was not epithelized in 12/88 (14%) patients of the main group (BTA) and 1/88 (1%) of the control group (LSS) ($p = 0.0006$). Among the above-mentioned 12 patients of the BTA group, spasm of the internal anal sphincter persisted in 2/12 (17%) patients, and no spasm was detected in the only patient from the LSS group ($p = 1.0$). All patients with unhealed wounds on the 60th day after surgery got local treatment with a drug containing human recombinant epidermal growth factor. Against the background of the treatment, the postoperative wound has epithelized within 2 weeks in 11/12 (92%) patients of the main group (BTA) and in 1 patient of the control group (LSS). In 1/12 (8%) patient of the BTA group, due to the ineffectiveness of the treatment and the absence of spasm of the internal anal sphincter, a scraping was taken from the wound to detect sexually transmitted diseases, and urea plasmas were detected by polymerase chain reaction (PCR), which required the prescription of antibacterial therapy taking into account the sensitivity of the pathogen. Against the background of ongoing treatment, the wound in this patient healed within one month.

On the 30th day after surgery, complaints of incontinence were noted by 28/88 (32%) patients of the main group and 27/88 (31%) patients of the control group ($p = 0.87$), the mean score on the Wexner scale in these patients on the 30th day was 2 (2; 3) and 3 (2; 3) points, respectively ($p = 0.3$). In both groups, the maximum score was 4 points, and the minimum score was 1 point. On day 60, this complication was observed in 6/88 (7%) patients of the BTA group and 10/88 (11%) patients of the LSS group ($p = 0.29$), and the mean score on the Wexner scale was 1 (1; 1) and 2 (1; 3) points, respectively ($p = 0.1$). In the control group (LSS), the maximum score on the Wexner scale on the 60th day after surgery was 4 points, and the minimum score was 1 point. It is worth noting that none of the patients had incontinence of liquid and solid stools, and the number of points during the follow-up gradually decreased in both groups. According to an independent, subjective assessment by patients

Table 6. *Factors associated with the development of transient AI on the 60th day after surgery*

Factor	OR (CI 95%)	p
Method of internal sphincter relaxation:		
BTA	1	
LSS	1.75 (0.61–5.05)	0.3
Surgery type		
Standard	1	
Extended	3 (1.06–8.52)	0.04
Age	1.03 (0.98–1.07)	0.22
BMI	1.02 (0.93–1.13)	0.64
Gender		
Male	1	
Female	0.9 (0.32–2.55)	0.85
Childbirth (N)		
0	1	
1	0.85 (0.14–4.9)	0.86
2	0.67 (0.12–3.92)	0.66
3 and more	3.25 (0.27–39)	0.35
Complicated childbirth		
No	1	
Yes	0.49 (0.06–4.18)	0.52

of the duration of temporary ASI according to the Wexner scale, in the main group the median indicator was 16 (5.5; 28) days, in the control group — 20 (9; 26) days ($p = 0.56$).

The intensity of postoperative pain in the compared groups did not differ both after defecation and during the day ($p > 0.05$). In the postoperative period, the use of analgesics was required by all patients, whose groups were comparable by the specific gravity as well as by the duration of taking painkillers ($p > 0.05$].

Overall hospital stay of inpatient treatment in both groups did not differ significantly and amounted to 5 (4; 6) days in the main group (BTA) and 4 (4; 6) — in the control group (LSS) ($p = 0.33$).

The time of temporary disability of patients after surgery in the main group (BTA) was 18.5 (9.5; 30.5) days, in the control group (LSS) — 22 (12; 31.5) ($p = 0.26$).

A univariant analysis of factors presumably influencing the risk of temporary anal incontinence on the 30th and 60th days after surgery was carried out. The expansion of the surgery extent turned out to be the only factor associated with a 2.44-fold increased chance of developing this complication on the 30th day of follow-up [p = 0.01] (Table 5).

The only factor influencing the ASI on the 60th day after surgery, as well as on the 30th, was the surgery type, the expansion of which increases the risk of developing temporary ASI by 3 times ($p = 0.04$) (Table 6).

As a result of a univariate analysis, it has been revealed that the use of BTA as a method of the internal anal sphincter relaxation is associated with a greater probability of delayed healing of a postoperative wound and increases its risk by 13.7 times ($p = 0.01$), and the expansion of the procedure type by 3.47 times ($p = 0.03$). In multivariate analysis, the above factors are also associated with an increased risk of this complication (Table 7).

A nomogram of the probability of postoperative wound healing is constructed depending on the surgery type and the method of the internal anal sphincter relaxation (Fig.3). When performing a BTA injection at a dosage of 40 units with the fissure excision, the effectiveness of treatment is 91%, and the expansion of the surgery type reduces this indicator to 74%. In turn, the positive result of treatment after LSS with fissure excision is 98%, and with the expansion of the surgery volume –97%.

Table 7. *Factors associated with an increase in the healing time of a postoperative wound*

Univariate analysis			Multivariate analysis	
Factor	**OR (CI 95%)**	**p**	**OR (CI 95%)**	**p**
Method of internal sphincter relaxation:				
LSS	1		1	
BTA	13.7 (1.7–108)	0.01	14.6 (1.8–116.7)	0.01
Surgeryvolume				
Standard	1		1	
Extended	3.47 (1.1–0.9)	0.03	3.82 (1.15–12.6)	0.03
Age	0.98 (0.94–1.04)	0.68	_	
BMI	0.94 (0.83–1.06)	0.32		
Gender				
Male	1			
Female	2.5 (0.67– 9.46)	0.17		
Persistent spasm of internal anal sphincter on the 60th day after surgery				
No	1			
Yes	0.84 (0.18–3.9)	0.83		

DISCUSSION

In literature, the incidence of fissure epithelialization in BTA and LSS is from 50.2% to 73.6% for neurotoxin, and from 85.8% to 95.7% for sphincterotomy [1,5,8]. Given the lack of ideas about the normal healing time of a chronic anal fissure during its treatment, which ranges from 14 days to 2 months, it is difficult to assess the effectiveness of the compared procedures [5,8,9]. In the study, the healing time of postoperative wounds was estimated within 60 days. This choice is due to the results of a study by E.E. Zharkov, according to which the epithelialization of wounds in the absence of specific wound infections was over 90% within 2 months after surgery [6]. During the indicated follow-up periods in the presented study, the healing rate in the main group (BTA) was 86%, in the control group (LSS) — 99%. At the same time, the addition of a drug containing human recombinant epidermal growth factor to the topical treatment increased the effectiveness to 99% in the BTA group and to 100% in the LSS group. Only one patient (8%) of the BTA group, due to the ineffectiveness of the treatment and the absence of spasm of the internal anal sphincter, required the antibacterial treatment due to the detection of ureaplasma according to PCR data, against which, within one month, the wound in this patient healed. Thus, when using the above drugs in the early postoperative period after injection of neurotoxin, it is possible to achieve treatment results comparable to sphincterotomy within 2 months.

The analysis of factors related to the healing of postoperative wounds showed that excision of a fissure with a fistula or in combination with procedures aimed at the concomitant hemorrhoidal disease (extended surgery type) increases the

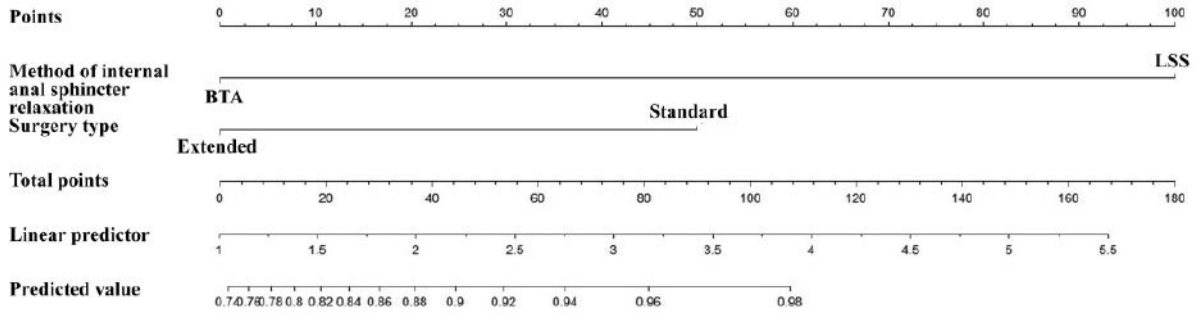

Figure 3. *Nomogram of the probability of healing of a postoperative wound on the 60th day after surgical treatment*

time of their epithelization, due to the larger area of the wound defect. This fact has not been investigated in literature before.

According to Russian guidelines, due to the presence of fibrosis in the area of a chronic anal fissure, its excision is performed in all cases [1]. However, in accordance with the ASCRS Guidelines for the CAF, foreign colleagues do not excise the chronic defect of the anoderm [10]. At the same time, there are no studies confirming or refuting the need to perform this procedure [1,5,8,10]. From our point of view, it is important to determine the normal healing time of the CAF, since an increase in the time of epithelization of the defect dictates the need to change the method of treatment of chronic anal fissure.

Within the framework of existing ideas about the pathogenesis of CAF, the compared methods of treatment are aimed only at eliminating its leading link — spasm of the internal anal sphincter [1,5,6,10,11]. In the study, it was possible to eliminate the increased sphincter tone in 79.6% of patients of the main group (BTA) and 86.2% of patients of the control group (LSS). Despite the persistent spasm of the sphincter in the remaining patients of both groups (18.2% in BTA and 14.8% in LSS), it did not affect the healing period of the postoperative wound. Unfortunately, the existing guidelines and randomized trials do not evaluate the relationship between the effectiveness of the treatment and the achievement of reference values of profilometry (APACR and MPACR).

At the same time, the assessment of the function of the internal anal sphincter is carried out using devices of various manufacturers, which causes high heterogeneity in the indicators [1,10]. In connection with the above, it is difficult to assess the effect of the persistent spasm of the internal anal sphincter on the epithelialization of the postoperative wound and the subsequent recurrence of the disease, which requires further studies.

The rate of temporary anal sphincter incontinence after LSS reaches 44% and occurs more often in comparison with the use of botulinum toxin, accompanied by temporary ASI in 0–19% of cases [5,8]. According to the study results, we did not receive a significant difference in the rate of this complication. The rate of temporary ASI on the 30th day of follow-up was 32% in the BTA group and 31% in the LSS group, 7% and 11% on the 60th day, respectively. The ASI rates by Wexner's scale were comparable in the both groups, clinically insignificant and gradually decreased over 60 days of follow-up.

In previous studies, we found that the risk of postoperative ASI increases in elderly patients (60 years or more), patients with clinical signs of perineal prolapse and females with a history of multiple and complicated childbirth (2 or more) [1,6,12–14]. In turn, according to the results of the study, an increase in the risk of temporary postoperative ASI, regardless of the method of relaxation of the internal anal sphincter, is due only to the extended type of surgery. This fact is fully explained by the greater probability of mechanical impact on the muscular structures of the anal sphincter with an extended surgery type, the presence of a larger wound surface in the anal canal, as well as the impact on internal hemorrhoids involved in the of involuntary anal continence.

CONCLUSION

The use of botulinum toxin type A at a dosage of 40 units after excision of the anal fissure is not inferior to lateral subcutaneous sphincterotomy in the effectiveness of eliminating of the spasm of the internal anal sphincter with a comparable rate of temporary anal sphincter incontinence within 2 months after surgery. Neurotoxin is an alternative to sphincterotomy. However, in some cases, it requires the addition of a topical drug containing human recombinant epidermal growth factor to the postoperative management.

RESEARCH PROSPECTS

There are a number of questions raised that require further study:

1. Determination of normal wound healing time after surgery for chronic anal fissure and indications for its excision.

2. Assessment of the risk of anal fissure recurrence in the long-term postoperative follow-up.

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