https://doi.org/10.33878/2073-7556-2020-19-1-80-99

THE TREATMENT OF CHRONIC ANAL FISSURES WITH FISSURE EXCISION AND BOTULINUM TOXIN TYPE A INJECTION (ISRCTN97413456)

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AIM: to assess the efficacy of botulinum toxin type A for chronic anal fissure.
PATIENTS AND METHODS: the study included 80 patients randomized by random number generation in 2 groups.
Forty patients underwent fissure excision in combination with injections of botulinum toxin type A into the internal sphincter (main group) and 40 – in combination with pneumatic balloon dilatation of the anal sphincter (control group).
RESULTS: there were no statistically significant differences in the intensity of pain after defecation and during the day between the groups, p=0.45 and p=0.39, respectively. The groups were comparable in the complications rate such as perianal skin hematomas (p=0.84), external hemorrhoid thrombosis (p=0.1), urinary retention (p=0.46), long-term non-healing wounds (p=0.76). Transitory weakening of the anal sphincter was significantly more often in the control group. On day 30, the transitory anal incontinence in the main group were observed in 6 (21%), in the control group – in 18 (75%) patients (p=0.0002). On day 60, the weakness of the anal sphincter remained in the main group in 3 (10.7%), in the control group – in 10 (41%) patients (p=0.02).
CONCLUSION: botulinum toxin type A and pneumatic balloon dilatation have equal effectiveness in the treatment of chronic anal fissure. The use of botulinum toxin type A can reduce the incidence of transitory weakening of the anal sphincter function in patients with chronic anal fissure.

[Key words: anal fissure, spasm of the internal sphincter, botulinum toxin type A, incobotulinum toxin A, pneumatic balloon dilatation]

For citation: 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; v. 19, no. 1 (71), pp. 80-99

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INTRODUCTION

Chronic anal fissure is a linear ulcerative defect of the anal canal that occurs due to trauma and further permanent spasm of the internal sphincter, leading to ischemia of the anoderm.

Due to the fact that the occurrence of a defect in the anal canal forms a pathogenetic circle, including an intense pain syndrome and spasm of the sphincter, its relaxation is a mandatory for any method of chronic anal fissure treatment.

The 'golden' standard for the elimination of spasm of the internal sphincter in world practice is a lateral subcutaneous sphincterotomy. The disadvantage of this method is the development of anal incontinence in some patients, which incidence is 8-30% [1-5]. In this regard, the search for the most optimal methods of relaxation of the anal sphincter, which do not lead to its irreversible damage, is currently continuing. In 1992, Sohn N. et al. proposed the anal sphincter pneumatic balloon dilatation [6]. Despite experimental studies by Li L. et al. indicating damage to the neuromuscular structures and the microcirculatory network of the anal sphincter in pneumatic balloon dilatation, the use of this method can reduce the incidence of anal incontinence to 12.5% in the early and 0% in the long-term postoperative follow-up [7]. However, it is quite obvious that it is possible to completely eliminate the risk of anal incontinence only in the absence of mechanical lesion on the anal sphincter. Thus, it was

decided to conduct a prospective randomized trial, the purpose of which is to improve the results of treatment of chronic anal fissure.

PATIENTS AND METHODS

The prospective, single-center, randomized study involving 80 patients with chronic anal fissure with sphincter spasm was performed in January 2017 – May 2019. Patients were randomized into groups by random number generation using a computer program. The main group consisted of 40 patients who underwent relaxation of the internal sphincter with botulinum toxin type A; the control group consisted of 40 patients who underwent pneumatic balloon dilatation of the anal sphincter according to the standard method.

The design was developed on the basis of a previous pilot study [8] (Fig. 1).

Inclusion criteria:

- patients with chronic anal fissure and spasm of the internal anal sphincter;
- age of patients 18-70 years old;
- informed consent of the patient to participate in the study;

Non-inclusion criteria:

- inflammatory diseases of the bowel;
- pectinosis;
- previous surgery on the anal canal;
- internal hemorrhoids III-IV grade;
- anal fistulas;
- anal incontinence (Wexner score is over 0);
- severe comorbidities;
- pregnancy and lactation;
- individual intolerance and hypersensitivity to botulinum toxin;
- myasthenia and similar syndromes.

Exclusion criteria:

- the need for sclerosing infection of internal hemorrhoids;
- patient's refusal to undergo control examination.

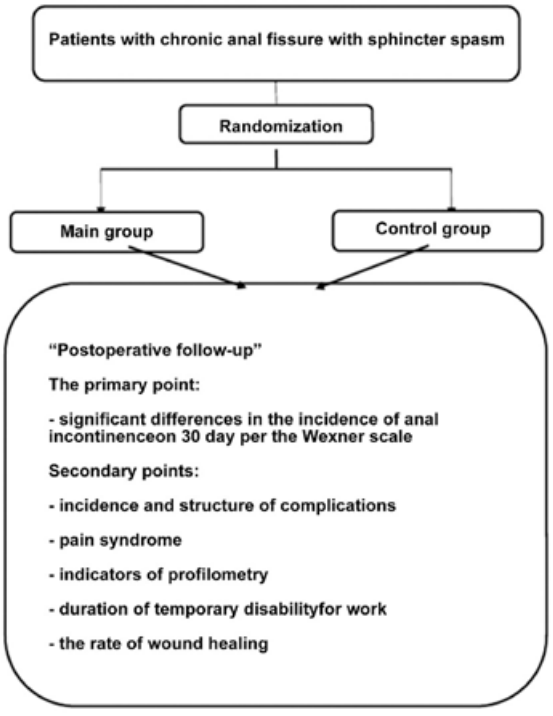

Figure 1. *Study design*

The primary end point of the study is to achieve significant differences in the incidence of anal incontinence on day 30 of the postoperative period. Secondary end points: the intensity of the pain syndrome after surgery; the incidence and structure of postoperative complications; the incidence and severity of weakening of the anal sphincter as per the Wexner scale on day 60; the duration of transitory postoperative incontinence; indicators of the continence according to profilometry before surgery and in the postoperative period on days 7 and 60; the incidence and time of wound healing.

All patients included in the study underwent profilometry: before the surgery, on the 7th and 60th days after the surgery. Before surgery and daily afterwards, the patients assessed the pain syndrome using VAS. On the 60th day, the results were evaluated, and the patients underwent anoscopy. For two months after the surgery, taking painkillers was assessed.

The patients in the main group after fissure excision were injected with botulinum toxin type A, free of complexing proteins, at 3 and 9 o'clock with 5 units of the drug (a total of 10 units) using an insulin 100-division syringe. The patients in the control group underwent fissure excision and pneumatic balloon dilatation of the anal sphincter according to the standard method [9].

In the future, for various reasons, 28 patients were excluded from the study. Twenty-eight patients of the main and 24 patients of the control groups met the Protocol and passed all tests, which allowed to reach the primary point of the study.

The groups were homogenous in the basic clinical characteristics (Table 1).

RESULTS

The intensity of the pain syndrome was comparable in the main and control groups and was 4.5 (1; 6) and 5 (2; 7) points after defecation (p=0.45), and 1 (0; 3) and 2 (0; 4) points during the day (Fig. 2) (p=0.39).

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

Indicator	Method of elimination of the internal sphincter spasm		*p*
	Botulinumtoxin (*n*=28)	Pneumatic balloon dilatation (*n*=24)	
The mean age	36 (32; 43.5)	42.5 (26; 53.5)	0.27
Gender:			
male	10 (35.71%)	10 (41.67%)	0.77
female	18 (64.29%)	14 (58.33%)	
Duration of the disease (months)	21 (7; 36)	21 (9.5; 66)	0.42
Number of fissures:			
One	23 (82%)	17 (71%)	0.42
Two	5 (18%)	6 (25%)	
Three	0 (0%)	1 (4%)	
Pain intensity after stool (Me, quartiles)	4.5 (1; 6)	5 (2; 7)	0.45
Pain intensity during the day (Me, quartiles)	1 (0; 3)	2 (0; 4)	0.46
Fibrous polyp			
One	10 (35.7%)	4 (16.7%)	0.26
Two	1 (3.6%)	2 (8.3%)	
Sentinel pile			
One	10 (35.7%)	4 (16.7%)	0.09
Two	2 (7.1%)	0 (0%)	
External hemorrhoids			
One	5 (17.9%)	6 (22.2%)	0.35
Two	2 (7.1%)	6 (22.2%)	
Three	4 (14.3%)	2 (7.4%)	
Defecation:			
Normal stool	20 (71.4%)	12 (50%)	0.15
Constipation	8 (28.6%)	12 (50%)	
Deliveries:			
0	7 (38.9%)	6 (42.9%)	0.33
1	9 (50%)	4 (28.6%)	
2	1 (5.6%)	3 (21.4%)	
3	0	1 (7.1%)	
4	1 (5.6%)	0	
History of complicated delivery	7 (38.9%)	2 (14.3%)	0.12
Anal incontinence (Wexner scale)	0	0	-

So, there were no significant differences in the intensity of pain after defecation and during the day between the groups.

Analgesics were required by 27 of 28 patients after botulinum toxin type A injection and by 23 of 24 patients after anal sphincter pneumatic balloon dilatation.

The median duration of taking analgesics in the group of botulinum toxin type A was 7 (4; 14), and in the control group of pneumatic balloon dilatation – 8 days (4; 16) (p=0.87).

There were no significant differences in the number of patients taking analgesics after surgery (Fig. 3).

On days 7 and 60, both groups showed a significant decrease in the maximal pressure in the anal canal at rest compared with the preoperative data (main group p=0.0003; controls p=0.002).

At the same time, there were no significant differences in maximal rest anal pressure between the groups (on 7th day p=0.32; on 60th day p=0.21) (Fig. 4).

There were also no significant differences in the distribution of patients by the level of maximal rest anal pressure on the 7th and 60th days of the postoperative period (Table 2).

Both in the main and in the control groups there was a significant decrease in the rest anal pressure on the 7th and 60th days of the postoperative period compared with the indicators before the surgery (p<0.0001 for both groups). As in the case of maximal rest anal pressure, the average pressure in the postoperative period did not differ significantly between the groups, (on 7th day, p=0.19; on 60th day, p=0.08) (Fig. 5).

Between the main and control groups there were no significant differences in the distribution of patients by the level of mean rest anal pressure on the 7th and 60th days after surgery (Table 3).

Thus, on the 60th day, spasm of the internal anal sphincter remained in 11 (21%) patients: in 8 patients

Table 2. *The level of maximal rest anal pressure on the 7th and 60th days*

The level of maximal rest anal pressure	Botulinum toxin type A (*n*=28)		Pneumatic balloon dilatation (*n*=24)		*p*	
	Д7	Д60	Д7	Д60	Д7	Д60
Increased (>112.2 mm Hg)	6 (21%)	8 (29%)	5 (21%)	3 (12,5%)	0.85	0.36
Normal (89.4-112.2 mm Hg)	10 (36%)	9 (32%)	7 (29%)	9 (37,5%)		
Decreased (<89.4 mm Hg)	12 (43%)	11 (39%)	12 (50%)	12 (50%)		

after administration of botulinum toxin type A, and in 3 patients after pneumatic balloon dilatation, p=0.36. The anal pressure with a voluntary contraction looked somewhat different. Both in the main and in the control groups, a statistically significant decrease in the maximal anal rest pressure was detected only on 7th day (p=0.0002 and p<0.0001, respectively), while by 60th it returned to the baseline in both groups (Fig. 6). There were no significant differences in the value of this data between the groups in the postoperative period, (on 7th day, p=0.2; on 60th day, p=0.15) (Table 4).

In contrast to the maximal pressure, the analysis of the mean anal pressure with a voluntary contraction showed that its significant decrease on the 7th day of the postoperative period is observed only after the anal sphincter pneumatic balloon dilatation (p<0.0001). After injection of botulinum toxin type A,

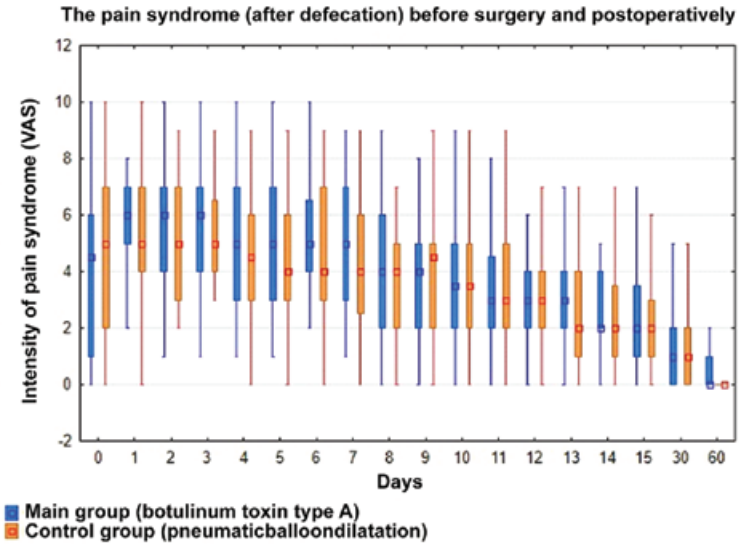

Figure 2. *Intensity of pain syndrome after defecation before surgery and in the postoperative period*

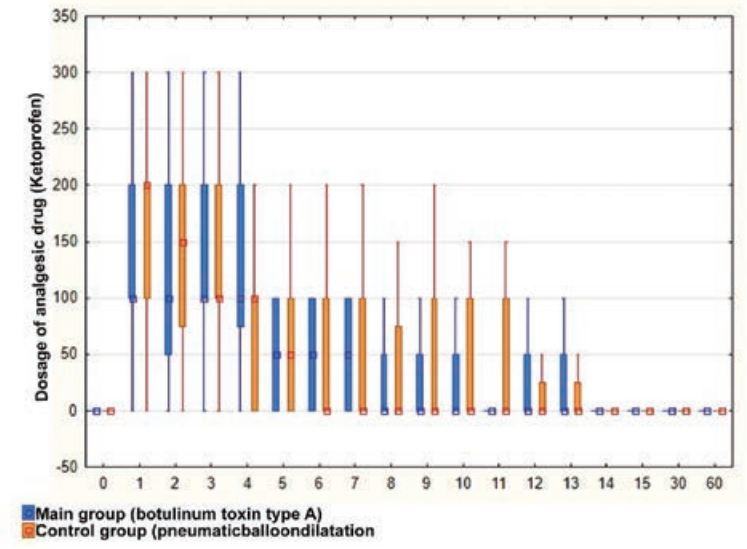

Figure 3. *The need for analgesics before surgery and in the postoperative period*

Table 3. *The level of mean anal rest pressure on the 7th and 60th days*

The level of mean anal rest pressure	Botulinum toxin type A (*n*=28)		Pneumatic balloon dilatation (*n*=24)		*p*	
	Д7	Д60	Д7	Д60	Д7	Д60
Increased (>60.4 mm Hg)	5 (18%)	8 (29%)	2 (9%)	3 (12%)	0.6	0.36
Normal (44.0-60.4 mm Hg)	9 (32%)	9 (32%)	9 (37%)	10 (42%)		
Decreased (<44.0 mm Hg)	14 (50%)	11 (39%)	13 (54%)	11 (46%)		

the mean anal pressure with voluntary contraction remains at the baseline level on the 7th and 60th days after surgery (p=0.66) (Fig. 7).

At the same time, the distribution of patients by the level of this indicator on the 7th and 60th days of the postoperative period did not differ significantly between the groups (Table 5).

The groups were comparable in the complications rate (perianal skin hematomas, external hemorrhoid thrombosis, urinary retention, long-term non-healing wounds) (p=0.76) (Table 6).

Postoperative anal incontinence on 30th day was noted by 6 (21%) patients of the main group, while in the control group in 18 (75%) people (p=0.0002).

The median score on the Wexler scale after botulinum toxin administration was 3 (2; 4) points, after pneu-

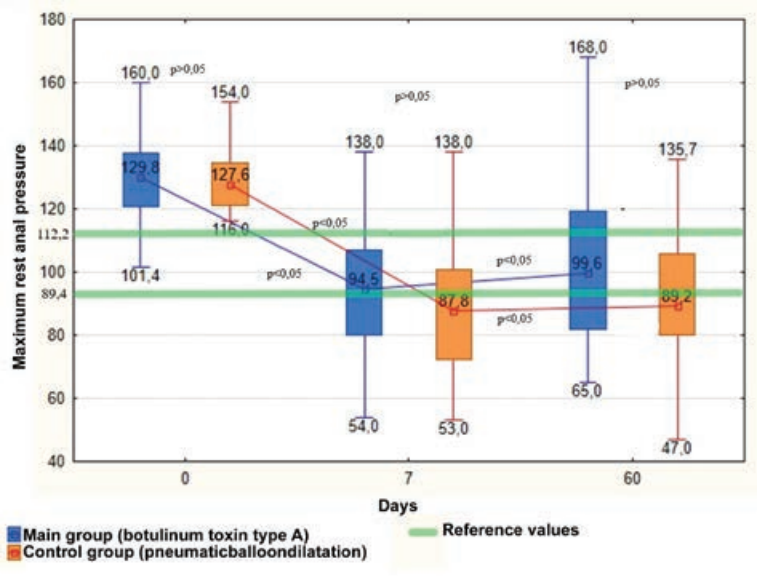

Figure 4. *Maximal rest anal pressure before surgery and in the postoperative period*

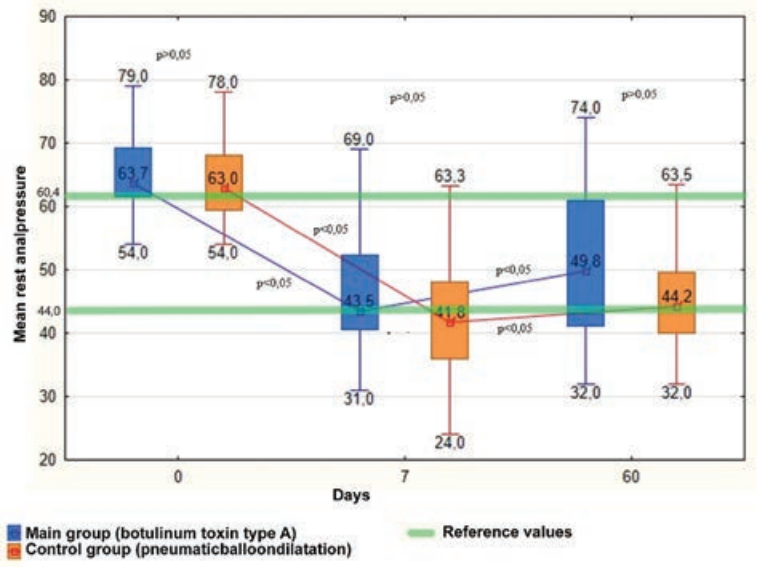

Figure 5. *Mean anal rest pressure before surgery and in the postoperative period*

Table 4. *The level of maximal anal pressure with a voluntary contraction on the 7th and 60th days*

The level of maximal pressure in the anal canal with voluntary contraction	Botulinum toxin type A (*n*=28)		Pneumatic balloon dilatation (*n*=24)		*p*	
	Д7	Д60	Д7	Д60	Д7	Д60
Increased (>149.7 mm Hg)	11 (39%)	17 (61%)	9 (37.5%)	19 (79%)	0.21	0.31
Norm (124.5-149.7 mm Hg)	12 (43%)	6 (21%)	6 (25%)	2 (8%)		
Decreased (<124.5 mm Hg)	5 (18%)	5 (18%)	9 (37.5%)	3 (13%)		

matic balloon dilatation – 3 (3; 6) points, (p=0.0003). The distribution of known risk factors for the development of transitory postoperative weakness of the anal sphincter among patients of the main and control groups on the 30th day of the postoperative period is presented in table 7.

Logistic regression was performed to identify factors that affect the development of transitory anal incontinence on the 30th day of the postoperative period (Table 8).

On 60th day, the transitory anal incontinence was noted by 3 (10.7%) patients of the main group and by 10 (41%) patients of the control group (p=0.02). In the main group, the score as per the Wexner scale was 3 (2;4) points, in the control group – 2.5 (2;5) (p=0.01).

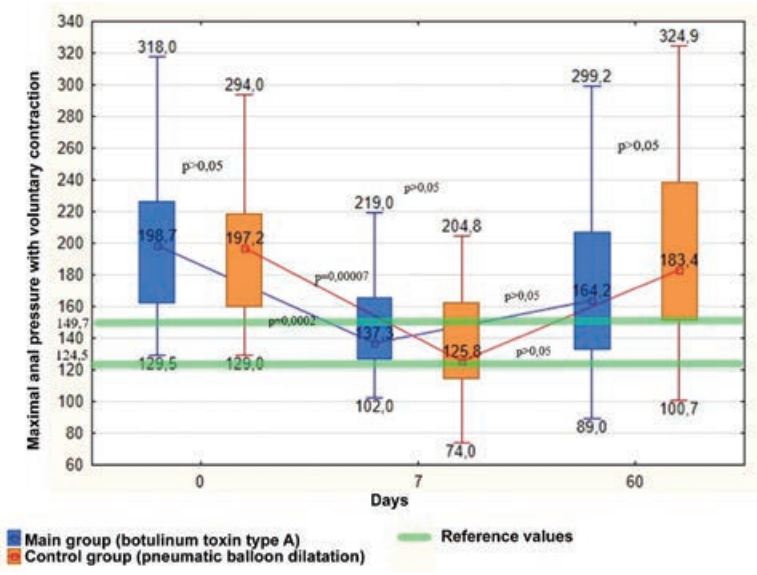

Figure 6. *Maximal anal pressure during voluntary contraction before surgery and in the postoperative period*

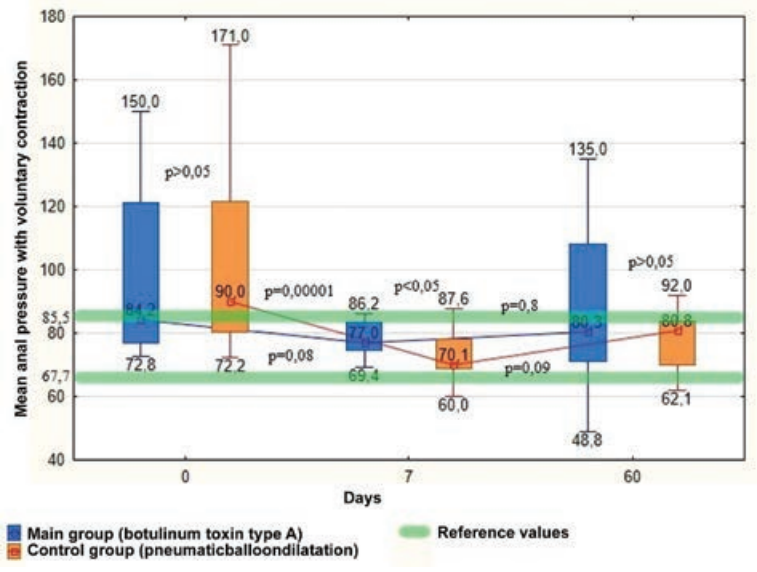

Figure 7. *Mean anal pressure during voluntary contraction before surgery and in the postoperative period*

Table 5. *The level of average pressure in the anal canal with an arbitrary contraction on the 7th and 60th days*

The level of average pressure in the anal canal with voluntary	Botulinum toxin type A (*n*=28)		Pneumatic balloon dilatation (*n*=24)		*p*	
	Д7	Д60	Д7	Д60	Д7	Д60
Increased (>85.5 mm Hg)	20 (71%)	16 (57%)	15 (62%)	17 (71%)	0.34	0.28
Norm (67.7-85.5 mm Hg)	6 (22%)	10 (36%)	4 (17%)	4 (17%)		
Decreased (<67.7 mm Hg)	2 (7%)	2 (7%)	5 (21%)	3 (12%)		

Table 6. *Postoperative complications rate*

Complications	Method of relaxation of spasm of the internal anal sphincter		
	Botulinum toxin type A (*n*=28)	Pneumatic balloon dilatation (*n*=24)	*p*
Hematoma	1 (3%)	2 (8%)	0.84
Thrombosis of external hemorrhoids	6 (21%)	1 (4%)	0.1
Urinary retention	0	1 (4%)	0.46
Long-term non-healing wound	10 (36%)	7 (29%)	0.76
Transient weakening of the anal sphincter function on day 30	6 (21%)	18 (75%)	0.0002
Transient weakening of the anal sphincter function on day 60	3 (10.7%)	10 (41%)	0.02

Table 7. *Risk factors of postoperative transient anal incontinence among patients of the main and control groups on the 30th day after surgery*

Risk factors for postoperative anal incontinence	Main group, *n*=28 (male 10, female 18)	Control group, *n*=24 (male 10, female 14)	*p*
Age >60	2 (7.1%)	4 (16.7%)	0.26
Multiple childbirths (over 2)	2 (11.1%)	4 (28.6%)	0.21
Complicated deliveries	7 (38.9%)	2 (14.3%)	0.12

Table 8. *Risk factors for transitory postoperative anal incontinence on the 30th day after surgery*

Risk factors for development of postoperative weakness of the anal sphincter	OR (CI 95%)	*p*
Method of treatment		
Pneumatic balloon dilatation	11 (3-40)	0.0002
Botulinum toxin type A	1	
Age of patients	1.0 (0.9-1.04)	0.89
Gender		
Female	2.1 (0.6-6.6)	0.2
Male	1	
Number of births	1.6 (0.6-3.8)	0.2
Complicated births		
Yes	1.8 (0.8-4.3)	0.13
No	1	

Risk factors for postoperative anal incontinence among patients of the main and control groups on the 60th day of the postoperative period are presented in table 9.

To identify the factors affecting the transitory postoperative anal incontinence, on the 60th day of the postoperative period, a logistic regression was performed, the results of which are presented in table 10.

Long-term non-healing wounds were detected in 10 (36%) patients of the main and 7 (29%) patients of the control group (p=0.76). In this case, spasm of the internal anal sphincter was detected in 5 (50%) patients of the main group and 1 (14%) patient of the control group (p=0.3). In other cases, the causes of non-healing of wounds were sexual infections in 5 (50%) patients of the main group and 4 (57%) patients of the control group. Another 1 (10%) patient of the main and 3 (43%) patients of the control group had no obvious cause of non-healing of wounds. The stimulators of healing processes assigned to patients allowed to achieve wound healing within 2 weeks in all cases.

DISCUSSION

Almost all contemporary methods of treatment of anal fissure are comparable in their effect on the pain syndrome, the need for painkillers, the nature and postoperative complications rate, as well as a number of other indicators taken into account when conducting research.

When evaluating the immediate results of treatment,

Table 9. *Risk factors for postoperative anal incontinence among patients of the main and control groups on the 60thday after surgery*

Risk factors for postoperative anal incontinence	Main group, *n*=28 (male 10, female 18)	Control group, *n*=24 (male 10, female 14)	*p*
Age >60	2 (7.1%)	4 (16.7%)	0.26
Multiple childbirths (over 2)	2 (11.1%)	4 (28.6%)	0.21
Complicated deliveries	7 (38.9%)	2 (14.3%)	0.12

Table 10. *Risk factors for transient postoperative weakness of the anal sphincter on day 60 after surgery*

Risk factor for postoperative anal weakness	OR (CI 95%)	*p*
Method of treatment		
Pneumatic balloon dilatation	6 (1.4-25)	0.015
Botulinum toxin type A	1	
Age of patients	1.04 (0.9-1.09)	0.11
Gender		
Female	4.7 (0.9-24.1)	0.06
Male	1	
Number of births	1.8 (0.8-4.3)	0.1
Complicated births		
Yes	2 (0.2-17)	0.52
No	1	

the main discussion revolves around two parameters: the wound healing rate and anal incontinence rate.

The method of treatment of chronic anal fissure, which allows to improve one of them, most often leads to the deterioration of the other and vice versa, whereas the sphincterotomy is the 'golden' mean.

In the study methods are homogenous in the intensity of pain syndrome, the need for painkillers, the effect on the internal anal sphincter function, the wound healing rate.

Unexpected was the fact that the wound healing rate after pneumatic balloon dilatation is lower than after sphincterotomy and is comparable to the same after the injection of botulinum toxin type A (p=0.76). On 60th day after the surgery, the anal fissure healed in 18 (64%) patients of the botulinum toxin type A group and in 17 (71%) of the pneumatic balloon dilatation group (p=0.76).

We think, that the main reason for this outcome is a worth vascularization in the postoperative wound area and the addition of a specific wound infection in some patients.

It is not possible to explain it completely this only by the presence of spasm of the internal sphincter, since it was detected only in 50% of the patients of the main and 14% of the control group (p=0.3) with non-healing wounds.

This assumption is supported by the fact that of the 8 patients of the main group and 3 patients of the control group (p=0.052), who according to the functional tests on the 60th day failed to eliminate the spasm of the internal anal sphincter, the wound did not heal in 5 patients in the main group and in 1 patient in the control group. In the remaining 5 patients (3 – in the main and 2 – in the control group) the anal wound healed despite the persisting spasm of the sphincter.

The above data allowed us to change the approach to treatment of patients with non-healing wounds.

As the first stage of treatment, all the patients were prescribed ointments containing recombinant epithelial growth factor.

This approach, despite the persisting spasm of the sphincter, led to the healing of postoperative wounds in 3 patients of the main group and 1 patient of the control group within 2 weeks.

Re-operation was required only for one patient with sphincter spasm, who was administered botulinum toxin type A in an increased dosage of up to 40 units without fissure excision, which allowed to eliminate the increased tone of the internal sphincter. Another patient developed a posterior transsphincteric anal fistula, but no spasm of the internal sphincter was detected according to profilometry. This patient underwent fistulectomy.

In both cases, it was possible to achieve postoperative wound healing within 2 months. In patients with wound infection without spasm of the sphincter, further inclusion in the treatment regimen of antibacterial therapy, taking into account the sensitivity of the microbs, allowed to achieve healing.

Thus, the ways to improve the effectiveness of treatment we see in elimination of internal anal sphincter spasm, including in the treatment drugs that affect healing processes, plastic closure of the wound defect after fissure excision (V-Y closure). However, these assumptions require further studies. Despite the fact that the groups did not differ in the postoperative morbidity, transitory anal incontinence was signifi-

cantly more often observed after performing pneumatic balloon dilatation. Given that the groups were comparable in terms of the main risk factors for the postoperative anal incontinence [10], this can be explained by the greater invasiveness of the pneumatic balloon dilatation [1,7,11].

According to the logistic regression, the development of transitory postoperative anal incontinence is associated only with the method of relaxation of the internal anal sphincter.

The chances of its development in patients who underwent the fissure excision with pneumatic balloon dilatation, on the 30th day 11 times higher than after the injection of botulinum toxin type A, OR 11 (3-40) p=0.0002, and on the 60th day – 6 times, OR 6 (1.4-25) p=0.015. The value of other factors are not significant. Obviously, pneumatic balloon dilatation has a more significant effect on the external sphincter function, which is indirectly confirmed by the results of functional tests.

Thus, a significant decrease in the mean anal pressure with voluntary contraction was observed only in the control group.

CONCLUSION

The use of botulinum toxin type A after excision of the anal fissure is similar to pneumatic balloon dilatation efficacy (the intensity of pain, the need for analgesics, the rate and time of wound healing) but has a less pronounced adverse effect on the function of the external sphincter of the rectum and reduces the anal incontinence rate after surgery.

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The authors declare no conflicts of interest.

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Received – 09.01.2020 *Revised – 17.01.2020* *Accepted – 20.01.2020*