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Effectiveness of 0.3% nifedipine gel combined with 2.0% lidocaine and BTA 80 U in treatment of chronic anal fissure. Pilot randomized study. Preliminary results.

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ABSTRACT *AIM: to improve the results of chronic anal fissure treatment.*
PATIENTS AND METHODS: the study included 22 patients randomized by random numbers generation method into 2 groups. Eleven patients were included in main group and were treated with 0.3% nifedipine + 2.0% lidocaine gel, 11 patients of the control group received injections of botulinum toxin A into the internal anal sphincter at a dose of 80 U (BTA 80).
RESULTS: by day 30, there was a decrease of maximal resting pressure in anal canal (MRPAC) in both the main and control groups [p = 0.015 and p = 0.004, respectively] and the average resting pressure in anal canal (ARPAC) [p = 0.01 and p = 0.02, respectively]. There was no difference between the groups in pain severity both after stool and during the day (p = 0.5 and p = 0.6, respectively). On day 60, the defect was epithelized in 6/11 (54.6%) patients of the study group and in 9/11 (81.8%) patients of the BTA 80 group [p = 0.36], respectively. The reason of treatment failure in 4/11 (36.4%) patients of the main group and 2/11 (18.2%) patients of the control group was a preserved internal sphincter spasm. It was found that these patients used a lower amount of the drug product — 2.2 (1.8; 2.5) mg/day compared to 2.4 (1.9; 2.7) mg/day in other patients. On the day 30 after surgical treatment, complaints about gas incontinence were registered in 1/11 (9.1%) patients of the main group and 1/11 (9.1%) patients of the control group [p = 1]. Such a complication as external hemorrhoid thrombosis occurred only in 1/11 (9.1%) patients in the BTA 80 group [p = 0.87].
CONCLUSION: the study results show that gel containing 0.3% nifedipine and 2% lidocaine produces an effect on the tone of the internal sphincter comparable to BTA. However, the lack of accurate dosage of the drug product and/or low patient compliance reduce the effectiveness of treatment and make the use of BTA preferable for medical relaxation of the internal sphincter.

KEYWORDS: *chronic anal fissure, CAF, internal sphincter spasm, botulinum toxin A, BTA, nifedipine, conservative treatment*

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

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INTRODUCTION

In recent years, there has been a trend in clinical practice to the growth of indications for surgery of chronic anal fissure (CAF), which is the reason for the search for new sphincter-saving and minimally invasive methods [1]. To date, among drug products for relaxation of the internal sphincter, studies have been done in Russia to assess the effectiveness of organic nitrates [2,3]. Current clinical guidelines provide a clear description of botulinum toxin A (BTA) for patients with chronic anal fissure [4]. However, the main problem with organic nitrates is the incidence of side effects and, as a result, low patient compliance. Besides, there are no official dosage forms of products with organic nitrates in Russia, and, therefore, there are no indications for their use

in national clinical guidelines [4]. At the same time, in recent years, modern combined products have appeared in Russia: 0.3% nifedipine and 2% lidocaine gel.

AIM

To assess the results of chronic anal fissure treatment.

PATIENTS AND METHODS

From January 2023, a randomized study included 22 patients with chronic anal fissure and spasm of the internal anal sphincter. Using randomization in a computer program by random number generation, the patients were divided into 2 groups. The main group included 11 patients who were treated with a combined product — 0.3% nifedipine + 2.0% lidocaine gel in accordance with the information leaflet (a small amount of gel was applied to the perianal skin and into the anus to a depth of 1 cm). The amount of the drug product used was controlled by weighing the tube on analytical scales before the start of use and at the end of treatment. The control group included 11 patients who received injections with botulinum A toxin into the internal anal sphincter at a dosage of 80 U according to the standard procedure in the clinical guidelines [4] (Fig. 1).

Inclusion criteria: patients with chronic anal fissure with verified spasm of the internal anal sphincter by profilometry; age of patients over 18 years; patient's informed consent to participate in the study.

Non-inclusion criteria: patients with a history of anal canal and rectal surgery (except for minimally invasive techniques); presence of anal incontinence stage 1–3 (Wexner scale score above 0 points); inflammatory bowel diseases; external and internal hemorrhoids of stage 3–4; anal fistula; severe comorbidities; fibrous polyp of the anal canal or sentinel tag with clinical manifestations; anal fissure complicated by fistula.

Exclusion criteria: anal fistula (detected intraoperatively); patient's refusal at any stage; noncompliance with the study protocol.

The groups were homogenous in general clinical characteristics: gender, age, time of disease, number of fissures, intensity of pain syndrome after stool and during the day, the presence of fibrous polyps of the anal canal and sentinel tags, external and internal hemorrhoids, type of defecation (Table 1). All patients underwent profilometry before the treatment, as well as on the days 30 and 60. Patients were assessed daily for pain syndrome according to the visual analog scale, as well as for the degree of anal incontinence by Wexner's scale. On days 30 and 60, digital rectal examination and anoscopy were performed to control the epithelialization of the anoderm defect.

RESULTS

The amount of the drug product (0.3% nifedipine + 2.0% lidocaine gel) used by patients during treatment was 2.4 (1.9; 2.7) mg per day. There was no significant difference in the intensity of pain syndrome between the main and control groups after defecation ($p = 0.5$) (Fig. 2).

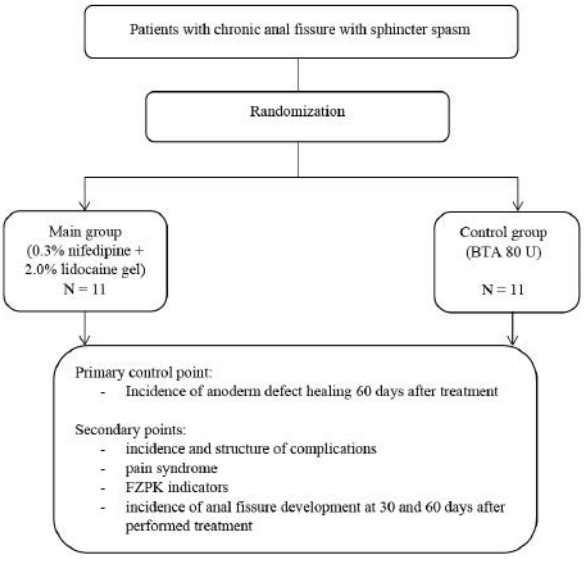

Figure 1. *Study design*

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

Parameter	Method of spasm elimination		*p*
	Main group (0.3% nifedipine + 2.0% lidocaine gel) *n* = 11	Control group (BTA 80) *n* = 11	
Median age	41 (34; 43)	37 (30; 51)	0.6
Sex:			
male	2 (18.2%)	3 (27.3%)	1.0
female	9 (81.8%)	8 (72.7%)	
Duration of disease (months)	8 (5; 24)	24 (8;36)	1.0
Number of fissures:			
One	10 (91%)	9 (81.9%)	1.0
Two	1 (9%)	2 (18.1%)	
Median pain after stool (quartiles)	4 (2; 6)	6 (1;8)	0.66
Sentinel tag			
One	1 (9%)	2 (18.1%)	0.5
Two	0 (0%)	1 (9%)	
Constipation	2 (22.2%)	7 (77.8%)	0.08

Table 2. *Distribution of patients according to the level of maximum resting pressure in anal canal 60 days after treatment*

Maximum resting pressure in anal canal	Main group (0.3% nifedipine + 2.0% lidocaine gel) *n* = 11	Control group BTA 80 *n* = 11	*p*
Increased (> 112.2 mmHg)	4 (36.4%)	3 (27.2%)	0.67
Normal (89.4–112.2 mmHg)	3 (27.2%)	5 (45.6%)	
Decreased (< 89.4 mmHg)	4 (36.4%)	3 (27.2%)	

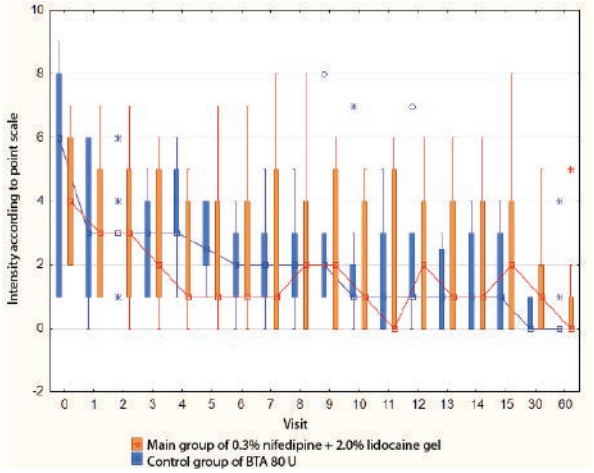

Figure 2. *The intensity of pain syndrome after defecation before and after treatment*

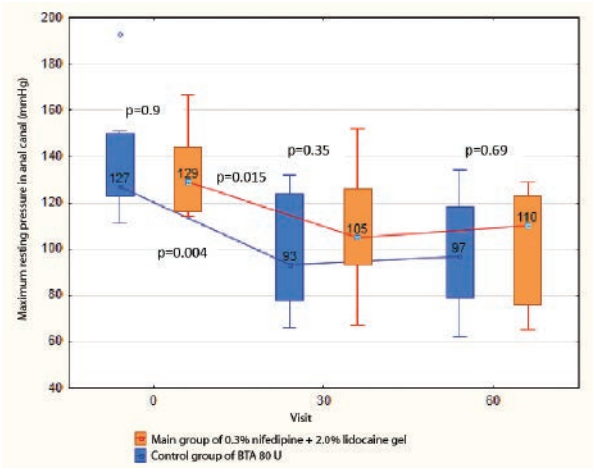

Figure 3. *Maximum resting pressure in anal canal before, on day 30, and on day 60 after the treatment*

Table 3. *Distribution of patients according to the level of average resting pressure in anal canal 60 days after treatment*

Average resting pressure in anal canal	Main group (0.3% nifedipine + 2.0% lidocaine gel) n = 11	Control group (BTA 80) n = 11	p
Increased (> 60.4 mmHg)	3 (27.2%)	3 (27.2%)	0.58
Normal (44.0–60.4 mmHg)	4 (36.4%)	6 (54.6%)	
Decreased (< 44.0 mmHg)	4 (36.4%)	2 (18.2%)	

By day 30, there was a significant decrease in the maximum resting pressure in anal canal (MRPAC) both in the main (0.3% nifedipine + 2.0% lidocaine gel) and in the control group (BTA 80), if compared with the baseline values [$p = 0.015$ and $p = 0.004$, respectively]. There were no differences between the groups [$p = 0.35$] (Fig. 3).

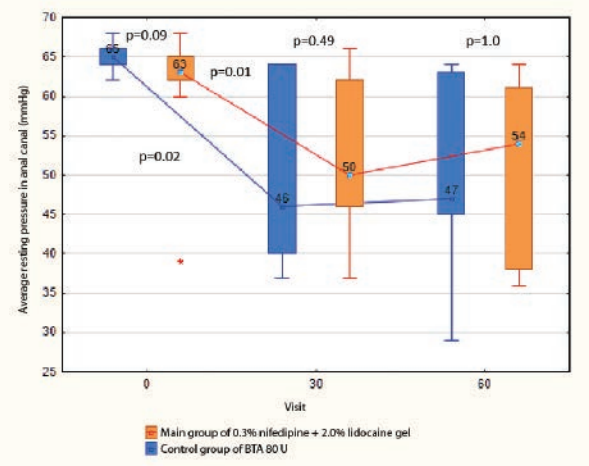

Figure 4. *Average resting pressure in anal canal before treatment, on day 30, and on day 60 after the treatment*

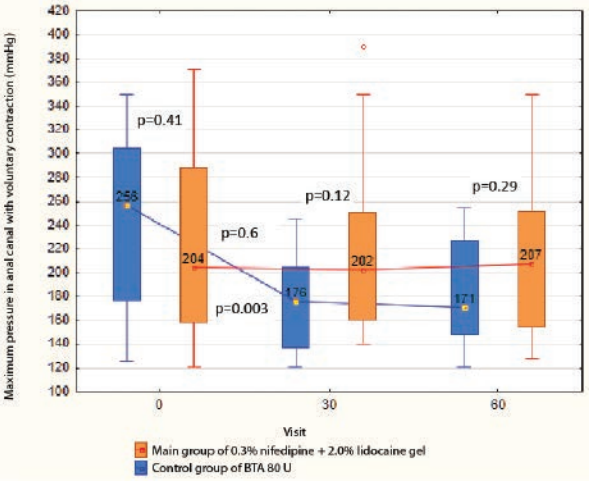

Figure 5. *Maximum pressure in anal canal with voluntary contraction before surgery and on days 30 and 60 after surgery*

The groups were comparable in anal maximum resting pressure on day 60 against the reference values [$p = 0.67$] (Table 2).

There was a significant decrease in mean anal resting pressure (ARPAC) by day 30 in patients in the groups [$p = 0.01$ and $p = 0.02$, respectively]. There were no differences in this parameter between the groups [$p = 0.49$] (Fig. 4).

According to the studied parameter, the groups were comparable on day 60 against the reference values [$p = 0.58$] (Table 3).

On the day 30 after the treatment, there was a significant decrease in the maximum pressure in the anal canal with voluntary contraction in the control group only (BTA 80) [$p = 0.003$]. However, there were no differences between the groups for the studied parameter [$p = 0.12$] (Fig. 5).

The groups were comparable against the reference values in maximum pressure in anal canal with voluntary contraction on day 60 [$p = 0.58$] (Table 4).

There were no differences between the main and control groups in the change of the mean pressure in anal canal with voluntary contraction by day 30 after treatment [$p = 0.3$], as well as by day 60 against the reference values [$p = 0.58$] (Table 5).

On the day 30 after the treatment, defect healing occurred in 2/11 (18.2%) patients of both the main and control groups [$p = 1$]. By the follow-up day 60, defect healing was detected in 6/11 (54.6%) patients of the main group and in 9/11 (81.8%) patients of the control group (Table 6).

The analysis of causes of treatment failure showed that 4/11 (36.4%) patients of the main group and 2/11 (18.2%) patients of the control group retained internal sphincter spasm. When

Table 4. *Distribution of patients according to the maximum pressure in anal canal with voluntary contraction on the day 60 after surgery*

Maximum pressure in anal canal with voluntary contraction	Main group (0.3% nifedipine + 2.0% lidocaine gel) *n* = 11	Control group (BTA 80) *n* = 11	*p*
Increased (> 149.7 mmHg)	9 (81.8%)	8 (72.7%)	0.58
Normal (124.5–149.7 mmHg)	2 (18.2%)	2 (18.2%)	
Decreased (< 124.5 mmHg)	0 (0%)	1 (9.1%)	

Table 5. *Distribution of patients according to the average pressure in anal canal with voluntary contraction on the day 60 after surgery*

Average pressure in anal canal with voluntary contraction	Main group (0.3% nifedipine + 2.0% lidocaine gel) *n* = 11	Control group (BTA 80) *n* = 11	*p*
Increased (> 85.5 mmHg)	3 (27.3%)	1 (9.1%)	0.58
Normal (67.7–85.5 mmHg)	8 (72.7%)	10 (90.9%)	
Decreased (< 67.7 mmHg)	0 (0%)	0 (0%)	

Table 6. *The timing of defect epithelialization*

Day	Treatment method		*p*
	Main group (0.3% nifedipine + 2.0% lidocaine gel) *n* = 11	Control group (BTA 80) *n* = 11	
30	2 (18.2%)	2 (18.2%)	1.0
60	6 (54.6%)	9 (81.8%)	0.36

Table 7. *The number of patients with transient anal incontinence before and after performed treatment according to the Wexner scale (norm = 0 points)*

Time points	The number of patients with transient anal sphincter insufficiency		*p*
	Main group (0.3% nifedipine + 2.0% lidocaine gel) *n* = 11	Control group (BTA 80) *n* = 11	
Preop	0	0	–
Day 30	1 (9%)	1 (9%)	1.0
Day 60	0	0	1.0

evaluating the use of the drug product, it was found that in 4/11 patients with spasm, compared with 7/11 patients without spasm, a slightly lower amount of the drug product used was noted [2.2 (1.8; 2.5) mg vs. 2.4 (1.9; 2.7) mg, $p = 0.7$]. Patients in the control group were treated locally with suppositories containing dioxomethyltetrahydropyrimidine. Along with this, a cytomegalovirus infection was detected in 1/4 patients of the main group in wound sampling. In order to eliminate spasm of the internal sphincter, BTA was administered at a dose of 80 U in 3 out of 11 (27.3%) cases in the main group on day 80. In 1 (9%) follow-up case in the main group and in 2/11 (18.2%) in the control group, lateral subcutaneous sphincterotomy (LSS) was performed on day 80. In all the above-described patients, the elimination of spasm of the internal sphincter and epithelialization of the anal fissure was achieved within a month after the treatment.

The remaining patient of the main group with cytomegalovirus infection was prescribed specific antiviral therapy, which also provided healing of the anal fissure within a month.

The anal incontinence in the form of gas incontinence on the day 30 after treatment occurred 1/11 (9%) patients of the main group and 1/11 (9%) patients of the control group [p = 1.0]. On day 60, no transient anal incontinence developed in both groups [p = 1.0] (Table 7).

One (9%) patient in the control group only had external hemorrhoids thrombosis [p = 0.87]. This complication was treated conservatively in accordance with clinical recommendations for the treatment of acute hemorrhoids.

DISCUSSION

The most significant characteristic of drug products used for medical relaxation of internal sphincter is the ability to reduce pressure in the anal canal at rest, which determines their clinical effectiveness in the treatment of anal fissure. The ability of BTA to reduce pressure in the anal canal was confirmed in a number of randomized studies [5,6,7], whereas functional results of the use of ointment forms of nifedipine are not so convincing. In most randomized studies, a physiological assessment of anal pressure was not performed [8,9,10]. Authors reported a significant decrease of the mean pressure in the anal canal at rest in a group of patients treated with 0.3% nifedipine and 2% lidocaine gel [11].

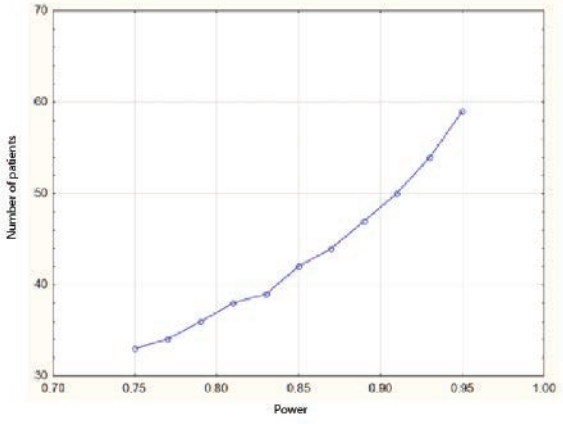

Figure 6. *Calculation of the planned study power*

According to the preliminary results of the study, the combined drug product (0.3% nifedipine + 2.0% lidocaine gel) results in a significant decrease in both mean and maximum pressure in the anal canal at rest. Despite the fact that this decrease is less significant than in the group of patients receiving BTA at a dose of 80 U, the differences between the groups do not reach significant values.

In addition to the ability to reduce the internal sphincter tone, each of the assessed drug products has its own characteristics. The indisputable disadvantage of nifedipine 0.3% + lidocaine 2% gel, like other ointment forms, is the inability to dose it accurately. Thus, if the dose of botulinum toxin A injected into the internal sphincter in all cases was 80 U, the amount of 0.3% nifedipine + 2% lidocaine gel used by patients during the day varied on the active substance (nifedipine) basis from 1.7 to 2.8 mg, averaging 2.4 (1.9; 2.7) mg. At the same time, in 4 patients of the main group with a non-healing anoderm defect and persistent spasm of the sphincter, the mean amount of the drug product used was 2.2 (1.8; 2.5) mg. Despite the absence of a significant difference in the amount of the drug product used in patients with persistent sphincter spasm and the rest of the patients in the study group, it can be stated that one of the reasons for the failure of 0.3% nifedipine + lidocaine 2% gel may be a decrease in the product dose due to the impossibility of its accurate dosing, or low patient compliance. With a comparable effect of drug products on the tone of the internal sphincter, BTA has advantages due to accurate dosing and the absence of the need for frequent repeated use. This confirms the fact of its successful use in 3 out of 4 patients of the main group with an unhealed anal fissure and persistent spasm of the internal sphincter. In this regard, it is very likely that with further recruitment of patients, these differences in the incidence of anal fissure epithelialization between the groups will reach significant values.

To achieve the primary control point of the study at 80% power and the difference between the incidence of anal fissure epithelialization in the main and control groups of 27.2% (p = 0.36), 37 patients should be enrolled into each group (Fig. 6).

In turn, the possible advantages of 0.3% nifedipine + 2% lidocaine gel include the presence of a local anesthetic in its formulation, which additionally contributed to pain relief. Despite this, according to preliminary data, the differences between the groups in terms of pain intensity did not reach statistically significant values. However, based on its dynamics, it is likely that they will be achieved along with further enrollment of patients.

CONCLUSION

The primary results of the study demonstrate that 0.3% nifedipine + 2% lidocaine gel has an effect on the tone of the internal sphincter comparable to BTA. However, further study is required for the final decision.

AUTHORS CONTRIBUTION

Study concept and design: *Evgeny E. Zharkov, Nikolay A. Goloktionov, Karina I. Sagidova, Ekaterina Yu. Lebedeva, Ivan V. Kostarev*

Collection and processing of materials: *Evgeny E. Zharkov, Nikolay A. Goloktionov, Karina I. Sagidova, Ekaterina Yu. Lebedeva*

Statistical processing: *Evgeny E. Zharkov, Nikolay A. Goloktionov*

Writing: *Evgeny E. Zharkov, Nikolay A. Goloktionov, Karina I. Sagidova, Ekaterina Yu. Lebedeva*

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