ORIGINAL SCIENTIFIC ARTICLE

COMPARISON OF DIFFERENT DOSES BOTULINUM TOXIN TYPE A EFFICACY IN CHRONIC ANAL FISSURE TREATMENT

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ABSTRACT

***Objective**: To compare the results of chronic anal fissure treatment with 10 IU and 40 IU botulinum toxin type A.*
***Patients and methods**: 56 patients were enrolled in case-control study divided into 2 groups consistent by the main clinical criteria. 28 patients in the study group had fissure excision in combination with 10 IU botulinum toxin type A (Xeomin) injection into internal anal sphincter, while 28 patients in control group received 40 IU product injections.*
***Results**: No statistically significant results in the pain assessment during the day and after bowel movement were obtained (p=0.41 and p=0.93, respectively). The groups were comparable by the frequency of complications such as transient anal incontinence, perianal skin hematoma, acute urinary retention (p>0.05). Complications such as thrombosis of external hemorrhoids and chronic non-healing wounds were most common in the study group (p=0.43 and p=0.0005, respectively). The product dose increase to 40 IU has a more significant effect on the functional treatment results (p=0.0053 and p=0.0002, respectively) and increases the odds for postoperative wound epithelialization 15-fold (p=0.01). Conclusion: 40 IU Botulinum toxin type A shows improvement in the treatment of chronic anal fissure without any increased risk of postoperative complications.*

***Keywords**: anal fissure, internal sphincter spasm, botulinum toxin type A.*

INTRODUCTION

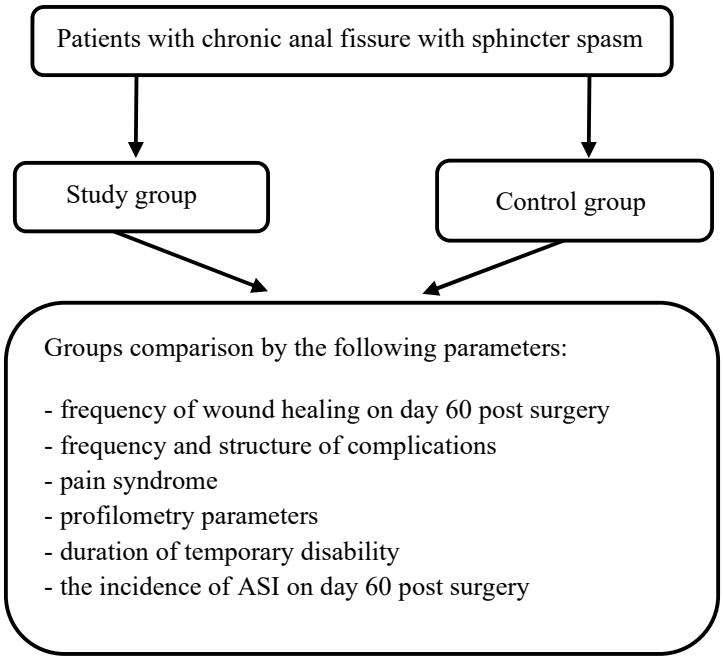
Chronic anal fissure (CAF) is a defect of anoderm with cicatricial-inflammatory changes indicating a long-lasting abnormality (1). The course of disease is characterized by intense pain syndrome usually occurring after the bowel movement. It is caused by internal anal sphincter (IAS) spasm, which underlies the pathogenesis of this condition impeding the defect healing (2-5). The IAS spasm elimination is therefore a pathogenetically justified method for treating patients with CAF (6). Various methods for drug relaxation of IAS (organic nitrates, calcium channel blockers, etc.) are currently available (7-9), however, the lateral subcutaneous sphincterotomy still remains the "gold" standard for CAF treatment (10,11). Persistent anal incontinence developing in some patients is a significant limitation of this method (12). Various authors have reported the development of this complication in 8-30% of patients (13-17). The attempts to replace the IAS excision with its dosed stretching have not improved the treatment results with the frequency of anal incontinence reported in the studies in the early and long-term postoperative period reaching 41% (18-20). Drug relaxation of IAS that does not result in persistent damage of anal sphincter is an alternative approach (7-9, 21).

Organic nitrates and calcium channel blockers are most commonly used for IAS spasm elimination. Both groups of drugs have a comparable efficacy and are not associated with IAS damage, however they induce side effects such as headache, orthostatic hypotension and require frequent and long-term use, which reduces the treatment compliance of the patients. Eventually, this results in a decreased efficacy and increased recurrence (7-9). Botulinum toxin type A (BTA) products are devoid of the above disadvantages; however the established recommendations for its use in CAF treatment are not available at the moment. In certain studies the authors suggest that there are no clinically significant differences between the BTA doses administered, and the product administration technique (22), while there are some authors stating the opposite (23). In this regard, it was decided to conduct a comparative study on the use of different doses of BTA in the treatment of chronic anal fissure with sphincter spasm.

MATERIALS AND METHODS

A case-control study enrolling 56 patients with CAF with IAS spams was conducted from 2018 to 2021 at A.N. Ryzhykh SMRC for Coloproctology. The study group included 28 patients who had fissure excision in combination with 5 IU BTA (Xeomin) injection into the internal anal sphincter at 3 and 9 hours (in total 10 IU); control group included 28 patients consistent with the study group by the common clinical characteristics: gender, age, disease duration, number of fissures, pain syndrome after bowel movement and during the day, fibrous polyps of the anal canal and sentinel piles, external and internal hemorrhoids, and the nature of bowel movements. 10 IU of the product into 4 points at 1.5, 7 and 11 hours (in total 40 IU) were injected in controls after fissure excision.

Figure 1. Study Design.



All patients enrolled in the study had profilometry prior to and on day 60 post surgery. Patients assessed their pain syndrome using visual analogue scale, and also the severity of anal incontinence using Wexner scale on a daily basis. On day 60 were performed: digital rectal examination, and anoscopy. The number and duration of pain medications use were recorded throughout the observation period.

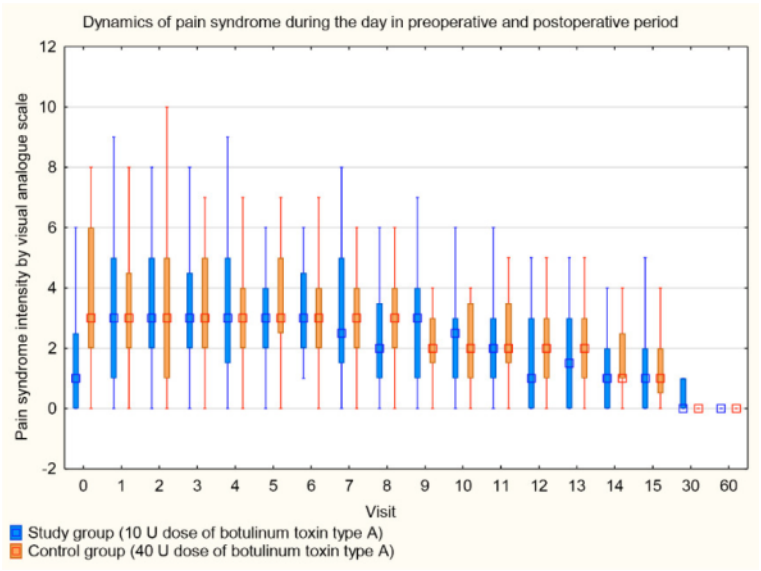
Table 1. Clinical and Functional Characteristics of Patients with Chronic Anal Fissure.

Parameter	**Spasm elimination method**		**p**
	10 IU Botulotoxin n=28	**40 IU Botulotoxin n=28**	
Median age	36 (32; 43.5)	34 (31; 43)	0.1
Gender: males females	 10 (35.71%) 18 (64.29%)	 11 (39. 29%) 17 (60. 71%)	0.5
Duration of disease (months)	21 (7; 36)	12 (6;28)	0.5
Number of fissures: One Two Three	 23 (82%) 5 (18%) 0 (0%)	 24 (85.7%) 4 (14.3%) 0 (0%)	0.5
Median pain after bowel movement (quartiles)	4.5 (1; 6)	5.5(4;7)	0.0702
Median pain during the day (quartiles)	1 (0; 3)	3 (2; 6)	0.063
Fibrous polyp One Two	 10 (35. 71%) 1 (3.57%)	 8 (28.57%) 0 (0%)	0.5
Sentinel pile One Two	 10 (35.71%) 2 (7.14%)	 9(32.14%) 0(0%)	0.3
External hemorrhoids One Two Three	 5 (17.86%) 2 (7.14%) 0 (0%)	 3 (10.71%) 1 (3.57%) 1 (3.57%)	0.58
Internal hemorrhoids			
One	2 (7.14%)	0 (0%)	0.08
Two	0 (0%)	0 (0%)	
Three	0 (0%)	3 (10.71%)	
Bowel movement: Normal stool Constipation	 20 (71.43%) 8 (28.57%)	 23 (82.14%) 5 (17.86%)	0.12
Anal sphincter incompetence by Wexner scale	0	0	-

RESULTS

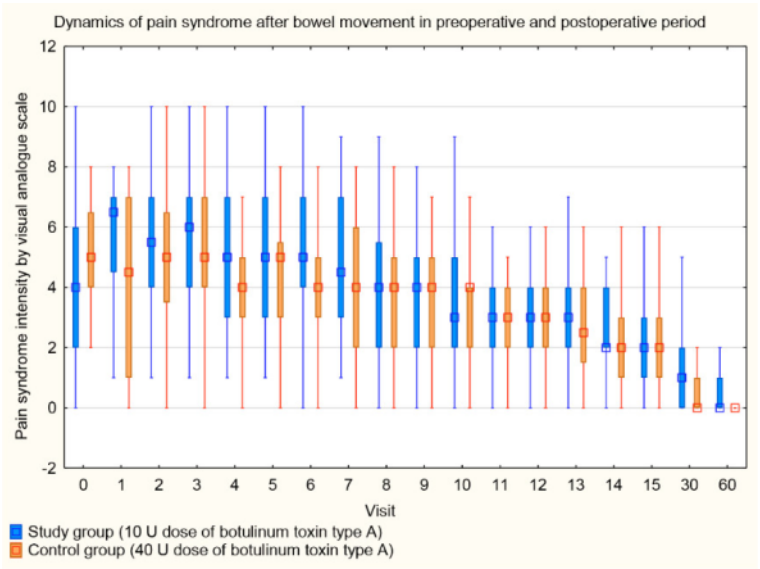
The intensity of pain syndrome after bowel movement and during the day was analyzed in the study and control groups.

Figure 2. Pain Syndrome Intensity During the Day in Preoperative and Postoperative Period.



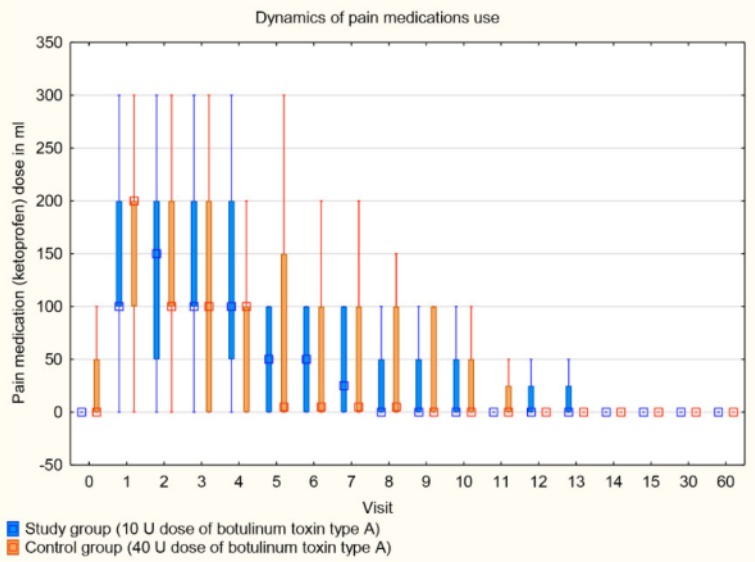
No clinically significant differences between the groups in the intensity of pain syndrome during the day were observed, p=0.41 (Fig. 2).

Figure 3. Pain Syndrome Intensity after Bowel Movement in Preoperative and Postoperative Period.



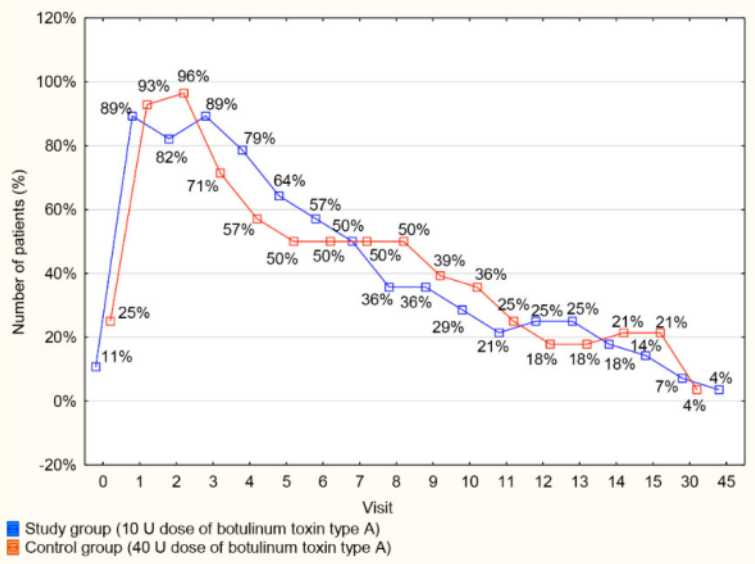
No significant differences between the groups in parameters and dynamics of pain syndrome after bowel movement were observed, p=0.93 (Fig. 3).

Figure 4. Need for Pain Medications Use in Preoperative and Postoperative Period.



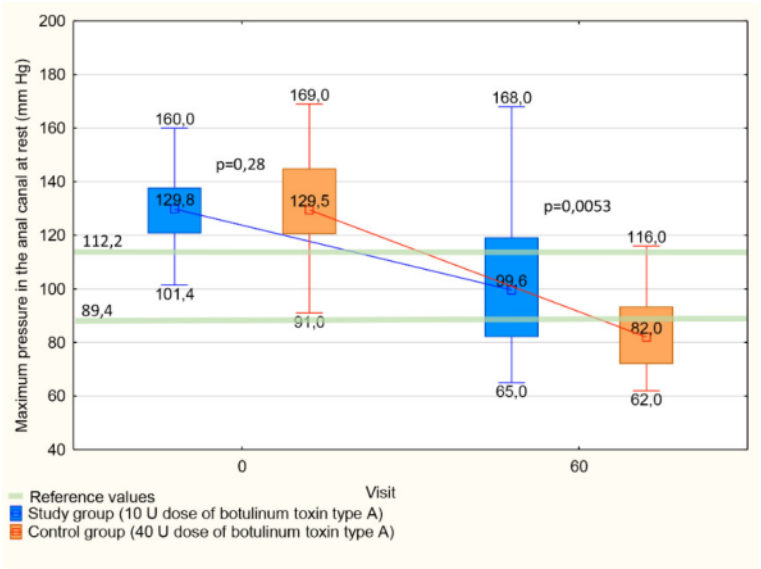
The duration of pain medications (ketoprofen) use and their dosage were assessed in postoperative period. No statistically significant differences in the assessment of these parameters were found, p=0.18 (Fig. 4).

Figure 5. Proportion of Patients (%) Taking Pain Medications in Preoperative and Postoperative Period.



No differences in the number of patients taking pain medications for 60 days post surgery were found, p=0.71. (Fig. 5)

Figure 6. Maximum Pressure in the Anal Canal at Rest Preoperatively and on Day 60 Post Surgery.



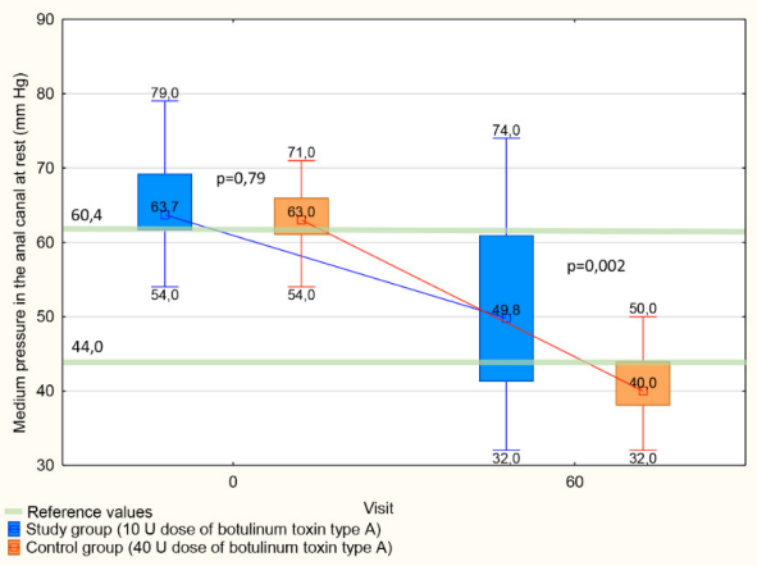
The maximum pressure in the anal canal at rest on day 60 post surgery was statistically significantly lower in control group, p=0.0053 (Fig. 6).

Table 2. Patients Distribution by Maximum Pressure Level in the Anal Canal at Rest 60 days Post Surgery.

Maximum pressure in the anal canal at rest	**10 IU Botulinum toxin type A group n = 28**	**40 IU Botulinum toxin type A group n = 28**	**p**
Increased (>112.2 mm Hg)	8 (29%)	2 (7%)	0.68
Normal (89.4 – 112.2 mm Hg)	9 (32%)	8(29%)	
Decreased (<89.4 mm Hg)	11 (39 %)	18 (64%)	

No statistically significant deviations of the studied parameter from the reference values on day 60 post surgery were found, p=0.68 (Table 2).

Figure 7. Medium Pressure in the Anal Canal at Rest Preoperatively and on Day 60 Post Surgery.



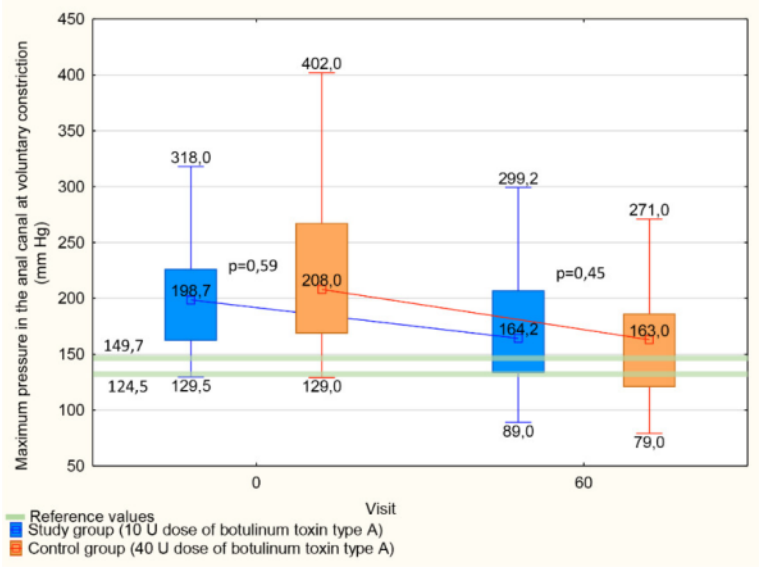
Medium pressure in the anal canal at rest on day 60 post surgery was statistically significantly lower in control group, p=0.002 (Fig. 7).

Table 3. Patients Distribution by the Medium Pressure Level in the Anal Canal at Rest 60 days Post Surgery.

Maximum pressure in the anal canal at rest	**10 IU Botulinum toxin type A group, n = 28**	**40 IU Botulinum toxin type A group, n = 28**	**p**
Increased (>60.4 mm Hg)	8 (29%)	0 (0%)	0.02
Normal (44.0-60.4 mm Hg)	9 (32%)	6(21%)	
Decreased (<44.0 mm Hg)	11 (39 %)	22 (79%)	

Statistically significant differences between the study and control groups in the medium pressure in the anal canal at rest on day 60 post surgery were observed, p=0.002 (Table 3).

Figure 8. Maximum Pressure in the Anal Canal at Voluntary Constriction Preoperatively and on day 60 Post Surgery.



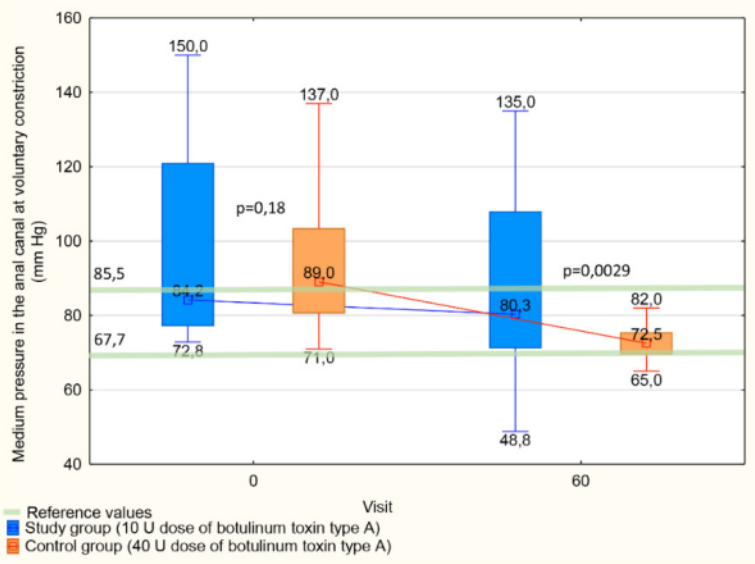
Whereas, the groups were comparable by the maximum pressure in the anal canal at voluntary constriction on day 60 post surgery, p=0.45 (Fig. 8).

Table 4. Patients Distribution by Maximum Pressure Level in the Anal Canal at Voluntary Constriction on day 60 Post Surgery.

Maximum pressure in the anal canal at rest	**10 IU Botulinum toxin type A group, n = 28**	**40 IU Botulinum toxin type A group, n = 28**	**p**
Increased (>149.7 mm Hg)	17 (61%)	16 (57%)	0.57
Normal (124.5–149.7 mm Hg)	6 (21%)	4(14%)	
Decreased (<124.5 mm Hg)	5 (18 %)	8 (29%)	

No statistically significant results for patients distribution by the level of maximum pressure in the anal canal were obtained, p=0.57 (Table 4).

Figure 9. Medium Pressure in the Anal Canal at Voluntary Constriction Preoperatively and on Day 60 Post Surgery.



Whereas, the medium pressure in the anal canal at voluntary constriction on day 60 post surgery was statistically significantly lower in control group, p=0.0029 (Fig. 9).

Table 5. Patients Distribution by Medium Pressure Level in the Anal Canal at Voluntary Constriction 60 Days Post Surgery.

Maximum pressure in the anal canal at rest	10 IU Botulinum toxin type A group, n = 28	40 IU Botulinum toxin type A group, n = 28	p
Increased (>85.5 mm Hg)	10 (36%)	3 (11%)	0.49
Normal (67.7–85.5 mm Hg)	16 (57%)	19(68%)	
Decreased (<67.7 mm Hg)	2(7 %)	6 (21%)	

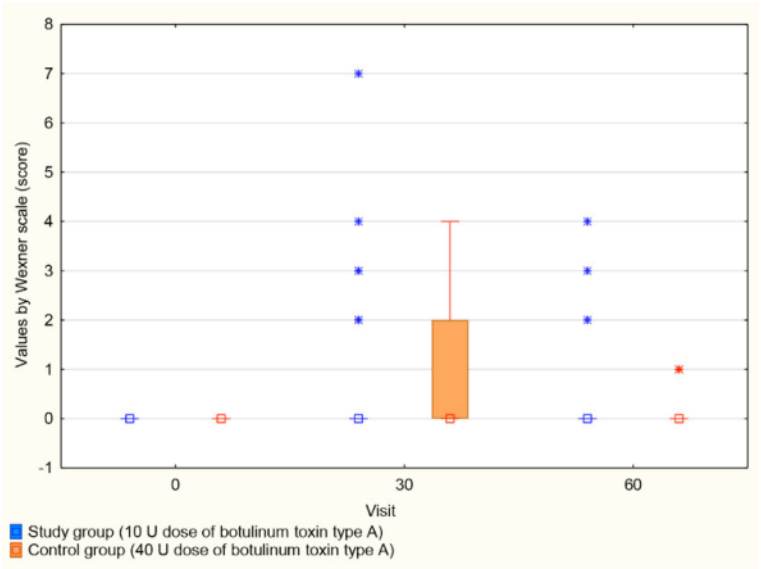
No statistically significant results for patients distribution by medium pressure level in the anal canal were obtained, p=0.49 (Table 5).

Table 6. Number of Patients with Preoperative and Postoperative Signs of Transient Anal Incontinence by Wexner scale (limit score = 0).

Period	Number of patients with signs of transient anal sphincter incompetence		p
	Study group, (n = 28)	Control group, (n = 28)	
Preoperative	0	0	-
Day 30	6 (21%)	10 (36%)	0.18
Day 60	3 (11%)	4 (14%)	0.5

Groups were compared by anal incontinence occurrence according to Wexner scale on day 30 and day 60, whereas the analysis has shown no significant results, p=0.18 and p=0.5, respectively (Table 6).

Figure 10. Assessment of Continence Function in Groups by Wexner Scale Preoperatively and 30, 60 Days Post Surgery.



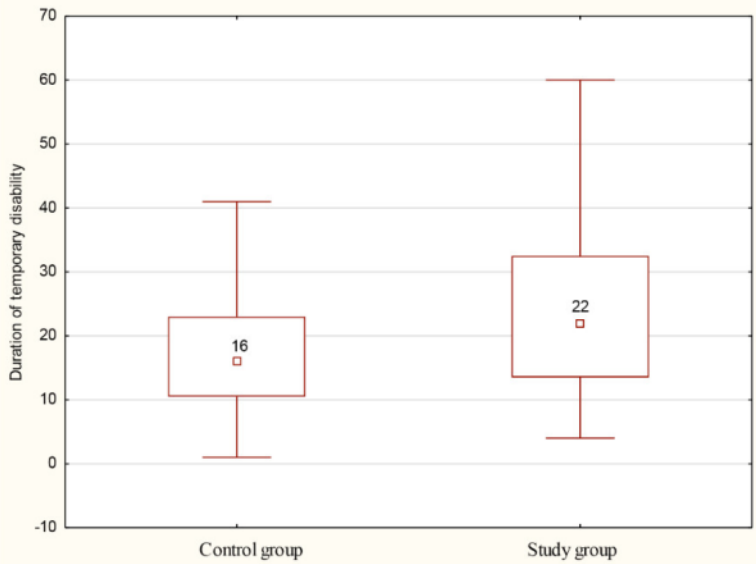
Assessment of transient anal incontinence severity by Wexner scale on day 30 and day 60 post surgery has shown no statistically significant results, p=0.93 and 0.37, respectively (Fig. 10).

Table 7. Frequency of Postoperative Complications.

Complications	**Method for IAS spasm relaxation**		**p**
	Study group (n = 28)	**Control group (n = 28)**	
Hematoma	1 (4%)	0(0%)	0.31
Thrombosis of external hemorrhoids	6(21%)	1(4%)	0.043
Urinary retention	0(0%)	0(0%)	1
Chronic non-healing wound	10(36%)	0(0%)	0.0005

Groups were comparable in terms of complications such as hematoma, and acute urinary retention (p=0.31 and p=1.0, respectively). However, thrombosis of external hemorrhoids (6 (21%) vs 1 (4%), p=0.043) and non-healing wounds (10 (36%), p=0.0005) were statistically significantly more common in the study group (Table 7).

Figure 11. Duration of Temporary Disability Following Treatment

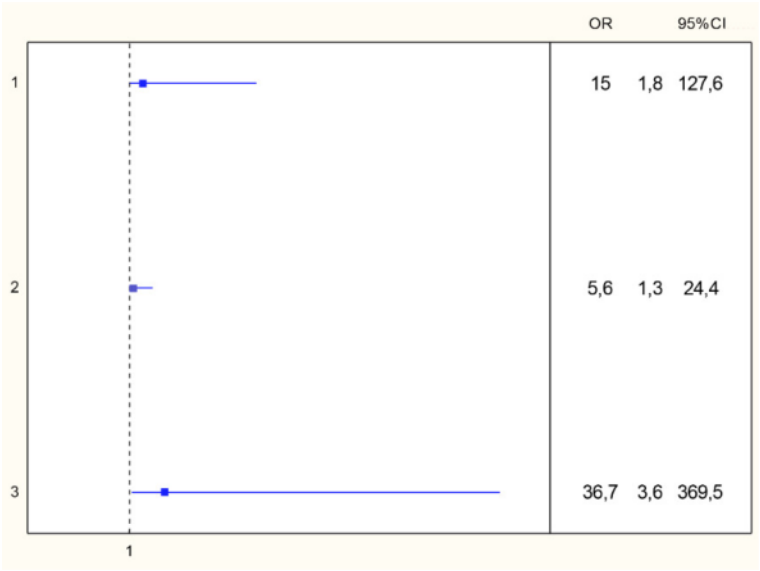


Groups were comparable by the duration of temporary disability, p=0.625 (Fig. 11).

Table 8. Risk Factors of Postoperative Chronic Non-Healing Wounds.

Risk factors	OR (CI 95%)	p
Treatment method: 40 IU Botulotoxin type A 10 IU Botulotoxin type A	 15(1.8-127.6) 1	0.01
Persistent sphincter spasm: Yes No	 5.6 (1.3-24.4) 1	0.02
Specific infections: Yes No	 36.7 (3.6-369.5) 1	0.002

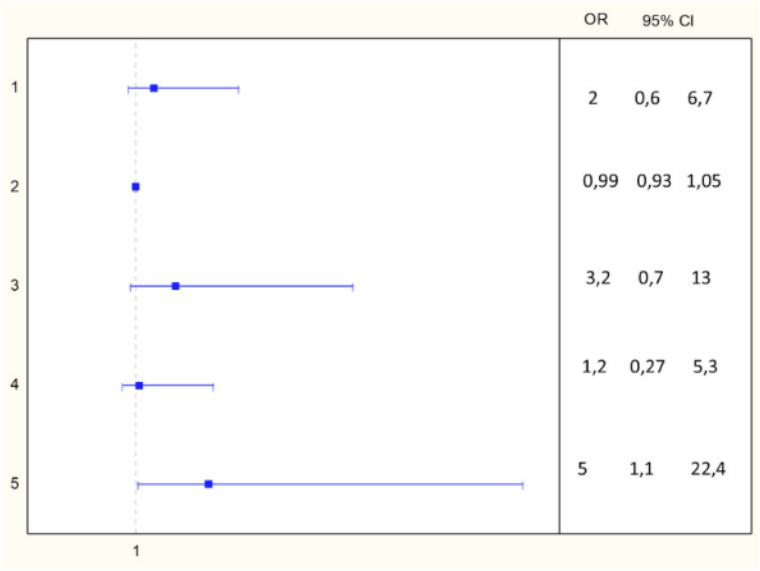
Figure 12. Factors Affecting the Period of Operative Wounds Healing.



Treatment method (10 IU Botulinum toxin type A/40 IU Botulinum toxin type A)
IAS spasm (Yes/No)
Specific wound infections (Yes/No)

As shown in Table 8 and Figure 12, the odds for non-healing of postoperative wounds is 5.6-fold higher with IAS spasm persisting on day 60 post surgery (p = 0.02), 15-fold higher with 10 IU BTA (p=0.01), and 36.7-fold higher with specific wound infections (p=0.002).

Figure 13. Factors Affecting Transient Anal Incontinence Occurrence on Day 30 Postoperatively.



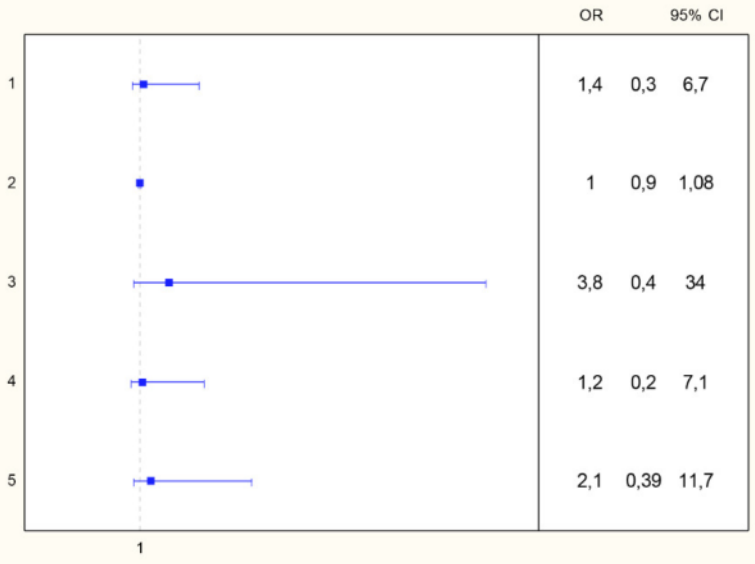
1. Treatment method (40 IU Botulinum toxin type A/10 IU Botulinum toxin type A)
2. Age
3. Gender (Females/Males)
4. Number of births (≥2/0-1)
5. Complicated labor (Yes/No)

Table 9. Factors Affecting Transient Anal Incontinence Occurrence on Day 30 Postoperatively.

Risk factors	OR (CI 95%)	p
Botulotoxin dose: 40 IU 10 IU	 2 (0.6-6.7) 1	0.24
Patients age	0.99 (0.93-1.05)	0.81
Gender: Females Males	 3.2 (0.7-13.0) 1	0.1
Number of births: 2 and more 0-1	 1.2 (0.27-5.3) 1	0.81
Complicated labor: Yes No	 5 (1.1-22.4) 1	0.035

Whereas, a history of complicated labor is the only factor that increases the odds for transient ASI occurrence on day 30 post surgery, p=0.035 (Table 9).

Figure 14. Factors Affecting Transient Anal Incontinence Persistence for 60 days in Postoperative Period.



1. Treatment method (40 IU Botulinum toxin type A/10 IU Botulinum toxin type A)
2. Age
3. Gender (Females/Males)
4. Number of births (≥2/0-1)
5. Complicated labor (Yes/No)

Table 10. Risk Factors Affecting Postoperative Transient Sphincter Ani Externum Incompetence Persistence for 60 days Post Surgery.

Risk factors	OR (CI 95%)	p
Botulotoxin dose: 40 IU 10 IU	 1.4 (0.3-6.7) 1	0.69
Patients age	1.0 (0.90-1.08)	0.97
Gender: Females Males	 3.8 (0.4-34.0) 1	0.23
Number of births: 2 and more 0-1	 1.2 (0.2-7.1) 1	0.88
Complicated labor: Yes No	 2.1(0.39-11.7) 1	0.38

No factors increasing the risk of transient anal incontinence occurrence on day 60 post surgery were observed (Table 10, Fig. 14).

DISCUSSION

A large number of publications on the use of BTA injection into the internal anal sphincter as a method for CAF treatment is currently available (7,22-24). However, the product doses and methods of administration are still unclear. According to Bobkiewicz et al., the increase in the doses and number of injection points has no effect on the treatment efficacy (22). On the other hand, according to O.V. Tkalich et al., administration of higher dose botulinum toxin and the increased number of injection points in recurrent patients helps to achieve stable IAS relaxation and CAF healing (19). This is supported by the results obtained by the authors in their study, where the increased doses of botulotoxin and changed administration technique helped to improve treatment efficacy. A 15-fold increase in BTA doses increases the odds for postoperative wounds epithelialization. To authors` opinion, this is due to a 5.6-fold increase in the odds for achieving stable IAS relaxation with 40 IU product injection, p=0.02.

An increase in the product doses and the number of injection points statistically significantly reduces the maximum and medium pressure in the anal canal at rest, thus considerably effecting the main pathogenetic mechanism of CAF – the IAS spasm (p=0.0053 and p=0.0002 , respectively). However, as profilometry data show, it is associated with more pronounced negative effects on the external sphincter function. Thus, the pressure in the anal canal at voluntary constriction is more significantly decreased in control patients.

Despite the fact that botulotoxin has no evident diffusion, the product is more likely to be delivered to the external rectal sphincter with the increased number of injection points. However, it should be noted that this negative effect does not affect the severity of clinical signs of transient anal incontinence, both on day 30 and day 60 postoperatively, p=0.18 and p=0.5, respectively (18). This again suggests that other factors play an essential role in anal incontinence development. Women, who had a history of complicated labor, are at 5-fold higher risk of anal incontinence, which indicates a hidden dysfunction of obturative rectum apparatus prior to surgery in this cohort of patients (12).

CONCLUSION

This study demonstrates that an increase in the product doses and number of injection points helps to improve treatment efficacy without negative effects on the incidence of complications, and, in particular, on transient anal incontinence occurrence. Taking into account the small number of patients and the comparative nature of the study, further increase in the product doses and changes in administration technique are still outstanding issues requiring further studies with randomization design.

CONTRIBUTION OF AUTHORS

Study concept and design: V.N. Kashnikov, A.A. Ponomarenko, I.V. Kostarev, E.E. Zharkov, O.V. Tkalich, S.V. Slozhenikin, E.A. Zagryadskiy, N.A. Goloktionov, R.Yu. Khryukin. **Materials collection and processing:** R.Yu. Khryukin, O.V. Tkalich, N.A. Goloktionov, S.V. Slozhenikin, E.A. Zagryadskiy, V.Yu. Medvedev, E.E. Zharkov , O.Yu. Fomenko, S.V. Nekhrikova, K.I. Arslanbekova, V.K. Misikov. **Statistical processing:** A.A. Ponomarenko, E.E. Zharkov , O.V. Tkalich N.A. Goloktionov, R.Yu. Khryukin, A.A. Akulov, A.S. Orlova. **Text writing:** N.A. Goloktionov, R.Yu. Khryukin, O.V. Tkalich, E.E. Zharkov, A.A. Akulov, A.S. Orlova. **Editing**: V.N. Kashnikov, A.A. Ponomarenko, I.V. Kostarev

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

REFERENCE

1. Titov A.Y., Zharkov E.E., Vardanjan A.V. Differential diagnosis for anal fissure and ulcerative lesions of anal canal and perianal skin. Koloproktologia, 2012. C.3-10.
2. Renzi A, Izzo D, Di Sarno G et al. Clinical, manometric, and ultrasonographic results of pneumatic balloon dilatation vs. lateral internal sphincterotomy for chronic anal fissure: a prospective, randomized, controlled trial. Dis Colon Rectum. 2008; 51(1): c.121-127. DOI: 10.1007/s10350-007-9162-7
3. Nasr M, Ezzat H, Elsebae M. Botulinum toxin injection versus lateral internal sphincterotomy in the treatment of chronic anal fissure: a randomized controlled trial. World J Surg. 2010; 34(11): c.2730-2734.
4. Valizadeh N, Jalaly NY, Hassanzadeh M et al. Botulinum toxin injection versus lateral internal sphincterotomy for the treatment of chronic anal fissure: randomized prospective controlled trial. Langenbecks Arch Surg. 2012; 397(7): c.1093-1098. DOI: 10.1007/s00423-012-0948-2
5. Magdy A, Nakeeb A, Fouda Y et al. Comparative study of conventional lateral internal sphincterotomy, V-Y anoplasty, and tailored lateral internal sphincterotomy with V-Y anoplasty in the treatment of chronic anal fissure. J Gastrointest Surg. 2012; 16(10): c.1955-1962. DOI: 10.1007/s11605-012-1984-5
6. Blagodarnyy L.A., Poletov N.N., Zharkov E.E. Pathogenesis of anal fissures. Koloproktologia. 2007; no. 1(19): pp. 38-41. (in Russ.)
7. Tkalich O.V., Zharkov E.E., Ponomarenko A.A. Modern methods of drug relaxation of the internal sphincter in patients with anal fissure. Khirurg. 2019; no. 8: pp. 26-42. (in Russ.).
8. Stewart DB, Gaertner W, Glasgow S et al. Clinical Practice Guideline for the Management of Anal Fissures. Dis Colon Rectum. 2017. T. 60, № 1: c.7-14. DOI: 10.1097/DCR.0000000000000735
9. Richard CS, Gregoire R, Plewes EA et al. Internal sphincterotomy is superior to topical nitroglycerin in the treatment of chronic anal fissure: results of a randomized, controlled trial by the Canadian Colorectal Surgical Trials Group. Dis Colon Rectum. 2000. T. 43, № 8: c.1048-57. DOI: 10.1007/bf02236548
10. Nasr M, Ezzat H, Elsebae M. Botulinum toxin injection versus lateral internal sphincterotomy in the treatment of chronic anal fissure: a randomized controlled trial. World J Surg. 2010. T. 34, № 11: c.2730-4. DOI: 10.1186/1471-230x-4-7
11. Shelygin Yu.A. Clinical recommendations. Coloproctology. Ed. Corresponding Member RAS Yu.A. Shelygin. M.: GEOTAR-Media, 2015, pp. 12-29. (in Russ.)
12. Shelygin Yu.A., Zharkov E.E., Orlova L.P. Risk of anal incontinence after anal fissure excision in combination with lateral subcutaneous sphincterotomy. Koloproktologia. 2005; no.1 (11), pp.10-16. (in Russ.).
13. Renzi A, Izzo D, Di Sarno G et al. Clinical, manometric, and ultrasonographic results of pneumatic balloon dilatation vs. lateral internal sphincterotomy for chronic anal fissure: a prospective, randomized, controlled trial. Dis Colon Rectum. 2008. T. 51, № 1: c. 121-7. DOI: 10.1007/s10350-007-9162-7
14. Valizadeh N., Jalaly N. Y., Hassanzadeh M. et al. Botulinum toxin injection versus lateral internal sphincterotomy for the treatment of chronic anal fissure: randomized prospective controlled trial. Langenbecks Arch Surg. 2012. T. 397, № 7: c. 1093-8. DOI: 10.1007/s00423-012-0948-2
15. Sohn N, Eisenberg MM, Weinstein MA et al. Precise anorectal sphincter dilatation--its role in the therapy of anal fissures. Dis Colon Rectum. 1992. T. 35, № 4: c. 322-7.
16. Stewart DB, Gaertner W, Glasgow S et al. Clinical Practice Guideline for the Management of Anal Fissures. Dis Colon Rectum. 2017. T. 60, № 1: c. 7-14. DOI: 10.1097/DCR.0000000000000735
17. Richard CS, Gregoire R, Plewes EA et al. Internal sphincterotomy is superior to topical nitroglycerin in the treatment of chronic anal fissure: results of a randomized, controlled trial by the Canadian Colorectal Surgical Trials Group. Dis Colon Rectum. 2000. T. 43, № 8: c. 1048-57. DOI: 10.1007/bf02236548
18. Tkalich O.V., Ponomarenko A.A., Fomenko O.Yu. et al. The treatment of chronic anal fissures with fissure excision and botulinum toxin type A injection (ISRCTN97413456). Koloproktologia. 2020; 19(1):80-99. DOI: 10.33878/2073-7556-2020-19-1-80-99
19. Yu. A. Shelygin, O. V. Tkalich, A. A. Ponomarenko. Follow-Up results of combination treatment of chronic anal Fissure. International Journal of Pharmaceutical Research. Jul - Dec 2020. Vol 12. DOI: https://doi.org/10.31838/ijpr/2020.SP2.040
20. Arslanbekova K.I., Khryukin R.Yu., Zharkov E.E. Anoplasty and lateral internal sphincterotomy for chronic anal fissure (systematic review and meta-analysis). Koloproktologia. 2020; 19(4): pp. 115-130. DOI: 10.33878/2073-7556-2020-19-4-115-130

21. Nekhrikova S.V., Titov A.Yu., Kashnikov V.N. Outpatient treatment of patients with diseases of the anal canal and perianal region. Dokazatel'naya gastroenterologiya. 2019; v.8, no. 3: pp. 27-37. (in Russ.)
22. Bobkiewicz A, Francuzik W, Krokowicz L et al. Botulinum toxin injection for treatment of chronic anal fissure: Is there any dose-dependent efficiency? A MetaAnalysis. World J Surg. 2016. DOI: 10.1007/s00268-016-3693-9
23. 23 M Mfnguez, F Melo, Al Espf et al. Therapeutic effects of different doses of botulinum toxin in chronic anal fissure. Dis Colon Rectum. August 1999.Vol. 42. № 8: c. 1016-1021. DOI: 10.1007/bf02236694
24. Khryukin R.Yu., Kostarev I.V., Arslanbekova K.I. et al. Botulinum toxin type a and lateral subcutaneous sphincterotomy for chronic anal fissure with the sphincter spasm. What to choose? (systematic literature review and meta-analysis). Koloproktologia. 2020; v. 19, no. 2(72), pp. 113-128 (in Russ.). DOI: 10.33878/2073-7556-2020-192-113-128.