https://doi.org/10.33878/2073-7556-2020-19-2-113-128

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)

Khryukin R.Yu.[1], Kostarev I.V.[1], Arslanbekova K.I.[2], Nagudov M.A.[1], Zharkov E.E.[1]

[1] Ryzhikh National Medical Research Centre for Coloproctology of the Ministry of Health of Russia, Moscow, Russia
(Director – academician of the Russian Academy of Sciences, professor Yu.A. Shelygin)
[2] Russian Medical Academy of Continuous Professional Education of the Ministry of Health of the Russian Federation, Moscow, Russia

INTRODUCTION: for the treatment of chronic anal fissure, various surgical techniques are used, the main difference between which is the method of eliminating the anal sphincter spasm. One of the most serious postoperative complications is the development of anal incontinence. To date, there are a number of methods for drug-induced relaxation of the internal sphincter, which can significantly reduce the risk of developing anal incontinence after surgery.
AIM: to evaluate the safety and effectiveness of botulinum toxin type A (BTA) and lateral subcutaneous sphincterotomy (LSS) in the treatment of chronic anal fissure with sphincter spasm.
MATERIALS and METHODS: a systematic review and meta-analysis of 7 selected randomized clinical trials comparing the results of treatment of chronic anal fissure using BTA and LSS was performed. The results of treatment of 489 patients were analyzed with an assessment of the following indicators: the incidence of epithelization of fissures, postoperative complications, development of anal incontinence and the disease recurrence.
RESULTS: In the BTA group, the incidence of fissure epithelization is 0.88 times lower than in the LSS group (OR=0.12; CI=0.06;0.22; p<0.00001). There were no statistical differences in the rate of postoperative complications in both groups (OR=1.07; CI=0.50;2.30; p=0.85). The risk of developing postoperative anal incontinence is 0.86 times lower in the BTA group than in the LSS group (OR=0.14; CI=0.03;0.64; p=0.01). The risk of relapse after lateral subcutaneous sphincterotomy is 6.06 times lower than when using botulinum toxin type A (OR=6.06; CI=3.52;10.42; p<0.00001).
CONCLUSION The use of botulinum toxin type A in the treatment of chronic anal fissure reduces the risk of developing postoperative anal incontinence, but this method is significantly inferior to lateral subcutaneous sphincterotomy in terms of the rate of chronic anal fissure epithelization.

[Key words: chronic anal fissure, lateral subcutaneous sphincterotomy, botulinum toxin type A, LIS, botox]

For citation: Khryukin R.Yu., Kostarev I.V., Arslanbekova K.I., Nagudov M.A., Zharkov E.E. 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

Address for correspondence: Khryukin R.Yu., Ryzhikh National Medical Research Centre for Coloproctology of the Ministry of Health of Russia, 2, Salyama Adilya street, Moscow, 123423; tel.: +7 (499) 199-04-09; e-mail: info@gnck.ru

INTRODUCTION

According to the literature, 30-40% of the population consult a doctor about proctological diseases during their lifetime [1-4].
At the same time, the incidence of chronic anal fissure (CAF) ranges from 20 to 23 per 1,000 adults [5,6], and the specific weight is from 10 to 15% [5,7-10].
A significant role in the etiology and pathogenesis of this disease belongs to the internal sphincter spasm [11-16], for the elimination of which Notaras, M. J. in 1969 proposed the method of lateral subcutaneous sphincterotomy (LSS, LIS – lateral internal sphincterotomy), which is the «gold» standard in the treatment of chronic anal fissure and is still widely used in clinical practice [15,17].
It is worth noting that all surgical methods of treatment of CAF, in which the elimination of anal sphincter spasm is performed in one way or another, are associated with the risk of postoperative anal incontinence

(AI), which varies according to a number of authors between 0 and 35% [18-20].

To reduce the risk of postoperative complications, methods of medicinal relaxation of the internal sphincter were proposed (nitrate preparations and calcium channel blockers of local action, botulinum toxin injection, etc.), in which no direct mechanical action is performed on the elements of the anal sphincter.

According to the literature, the use of botulinum toxin type A (BTA, botox) is accompanied by a lower recurrence rate and side effects than the use of other drugs for medicinal relaxation of the internal sphincter [21,22].

The literature presents a large number of studies on the comparison of methods of surgical and medicinal relaxation of the internal sphincter.

The subject of this systematic review and meta- analysis is the summation and statistical processing of data from all available randomized clinical trials comparing the efficacy and safety of botulinum toxin type A and lateral subcutaneous sphincterotomy in the treatment of chronic anal fissure.

MATERIALS AND METHODS

The systematic review and meta-analysis were performed in accordance with the international recommendations of the preferred reporting items for systematic reviews and meta-analyses check list (PRISMA) [23]. The search for publications was conducted in the electronic database of medical literature Medline and ended on 13.11.2019. The search query included the following terms: «anal fissure», «fissure in ano», «botulinum toxin», «botulinum toxin injection», «sphincterotomy», and «lateral internal sphincterotomy».

Restrictions on the date of publication of articles and language restrictions were not applied.

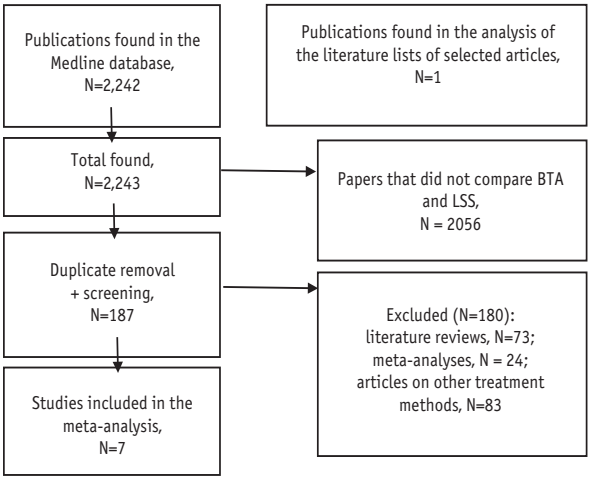


Figure 1. *Flow-chart for searching literature sources*

Criteria for selecting publications to be included in the review:

- full-text articles containing data from randomized clinical trials;
- studies comparing lateral subcutaneous sphincterotomy and botulinum toxin type A in the treatment of chronic anal fissure.
- the duration of patient follow-up is at least 4 months.

Additionally, a search for publications in the literature lists of selected studies for undiscovered sources was performed during the initial search.

Indicators of interest:

1. Rate of fissure epithelization.
2. Rate of complications.
3. Rate of development of anal incontinence in the postoperative period.
4. Recurrence rate.

Statistical data processing when comparing the above indicators was performed in the Review Manager 5.3 program. For all dichotomous data, the odds ratio (OR) was calculated with 95% CI. Statistical heterogeneity among the studies was evaluated using the χ^2 test, with $p<0.1$ and $I^2>50\%$ heterogeneity was considered statistically significant.

Results of search

After making a query in the PubMed search system, 2,242 publications were found in the Medline database.

At the next stage, the following were excluded: literature reviews – 73 articles, meta-analyses – 24 publications, studies on other methods of treating anal fissure – 83 publications.

In the literature lists selected for the analysis of articles, 1 additional publication was identified.

As a result, the analysis included 7 randomized clinical trials (Fig. 1).

The characteristics of publications are shown in table 1.

Data on 489 patients were analyzed, of which 248 (50.7%) were injected with botulinum toxin type A into the internal anal sphincter and 241 (49.3%) underwent lateral subcutaneous sphincterotomy.

The quality of the articles included in the meta-analysis was evaluated in accordance with the Cochrane risk of bias check list [24]. The results of research quality assessment are shown in figure 2. The low risk of rejection of results in more than 75% of publications is determined only by the research reporting criteria.

In turn, criteria for randomization method, blinding performers and researchers, distribution of patients by groups and completeness of description of the

Table 1. *Characteristics of studies comparing the use of botulinum toxin type A and lateral subcutaneous sphincterotomy in the treatment of chronic anal fissure*

Author	Year	Country	Follow-up period (months)	BTA dose (units)	Method	Number of patients	Postoperative wound healing, N	Complications, N	Postoperative AI***, N	Relapses, N
Mentes et al.	2003	Turkey	12	20	BTA*	61	46	0	0	7
					LSS**	50	47	0	8	2
Iswariah et al.	2005	Australia	6,5	20	BTA	17	7	N/A	N/A	9
					LSS	21	19	N/A	N/A	2
Massoud et al.	2005	Iran	6	20	BTA	25	22	5	N/A	5
					LSS	25	25	2	N/A	2
Arroyo et al.	2005	Spain	36	25	BTA	40	18	1	0	12
					LSS	40	37	2	2	2
Abd Elhady et al.	2009	Egypt	60	40	BTA	40	нд	3	0	21
					LSS	40	нд	2	0	4
Nasr et al.	2010	Egypt	4,5	20	BTA	40	25	8	0	16
					LSS	40	36	8	2	5
Valizadeh et al.	2012	Iran	12	50	BTA	25	12	0	0	12
					LSS	25	23	3	1	3

** BTA – botulinum toxin type A; ** LSS – lateral subcutaneous sphincterotomy; *** AI – anal incontinence*

treatment results have a low risk of bias less than 25% of the publications that questioned the quality of included in the meta-analysis studies.

RESULTS

Meta-analysis of the rate of fissure epithelization

Data on the healing rate are presented in 6 studies.
Meta-analysis of data revealed that when botulinum toxin type A is injected into the internal sphincter, the rate of healing of defects is 0.88 times lower than when performing lateral subcutaneous sphincterotomy (OR=0.12; CI=0.06;0.22; p<0.00001). When evaluating the homogeneity of groups in publications, it was found that there are significant biases I^2=0%, p=0.80 (Fig. 3A).

Meta-analysis of postoperative complications

6 studies provide data on postoperative complications. There were no statistically significant differences in the rate of postoperative complications after treatment of chronic anal fissure using botulinum toxin type A and lateral subcutaneous sphincterotomy (OR=1.07; CI=0.50;2.30; p=0.85).
Studies are heterogeneous I^2=0%, p=0.44 (Fig. 3B).

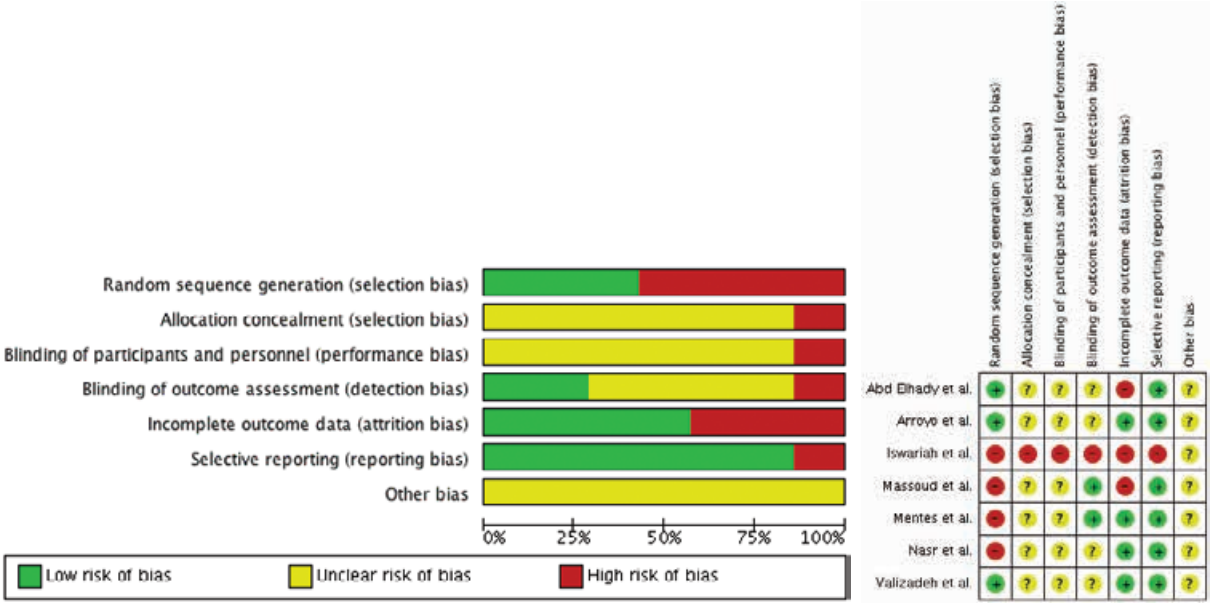


Figure 2. *Assessment of bias risk in studies comparing LSS (LIS – lateral internal sphincterotomy) and BTA (Botox) in the treatment of chronic anal fissure, according to the Cochrane risk of bias check list*

Meta-analysis of the development of postoperative anal incontinence

5 studies present data on the development of postoperative anal incontinence after performing the compared methods of treatment of chronic anal fissure.

It was found that the risk of developing postoperative anal incontinence is 0.86 times lower when using BTA than when performing LSS(OR=0.14; CI=0.03;0.64; p=0.01).

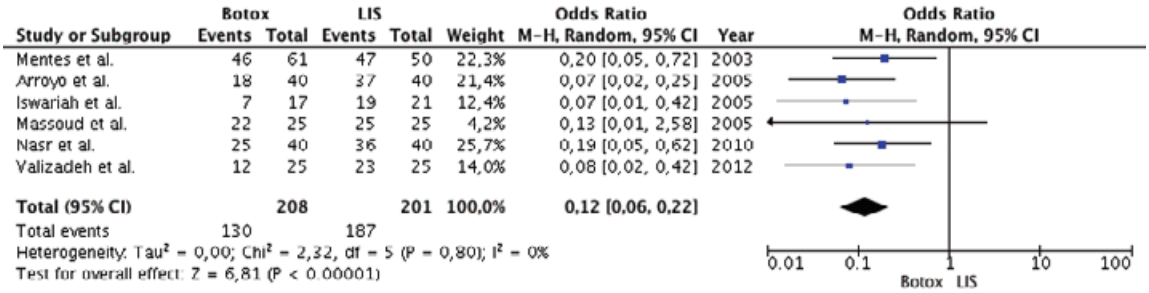
When analyzing the homogeneity of studies, their heterogeneity is noted I^2=0%, p=0.78 (Fig. 3C).

Meta-analysis of the recurrence rate

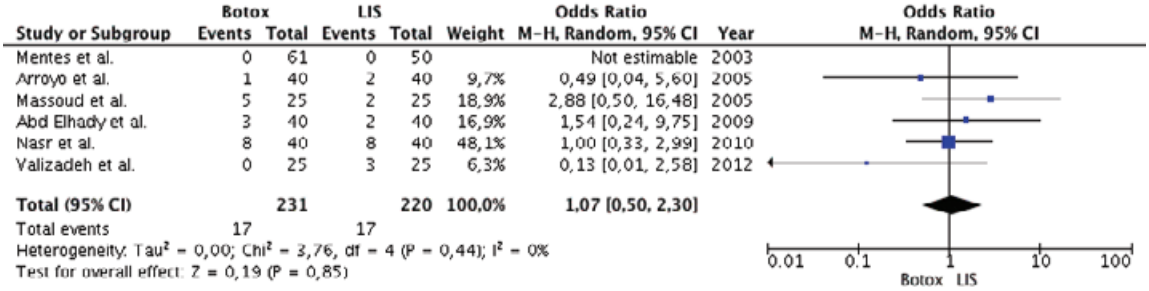
All 7 publications included in the meta-analysis have data on the recurrence rate after surgery.

The analysis revealed that the risk of relapse after lateral subcutaneous sphincterotomy is 6.06 times lower than when using botulinum toxin type A (OR=6.06; CI=3.52;10.42; p<0.00001).

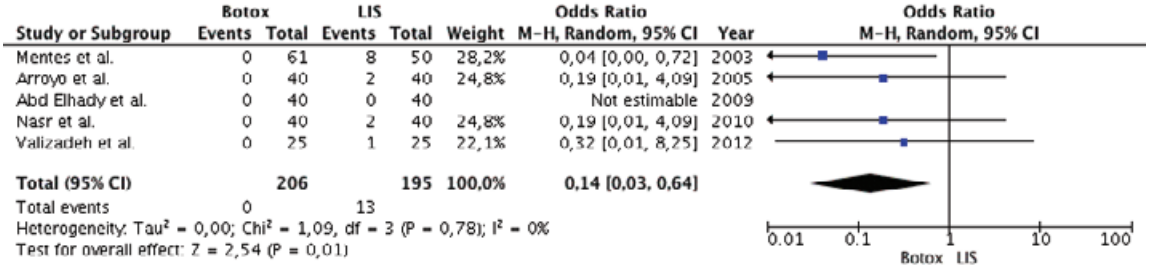
The analysis of publications for homogeneity revealed their significant heterogeneity I^2=0%, p=0.84 (Fig. 3D).



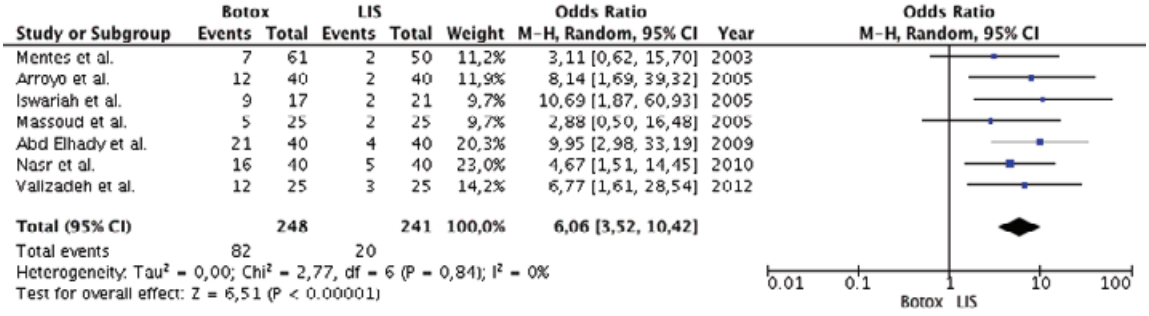
A. Rate of fissure epithelization in the treatment of CAF using BTA (Botox) and BPS (LIS)



B. Rate of postoperative complications in the treatment of CAF using BTA (Botox) and LSS (LIS)



C. Rate of postoperative AI development in the treatment of CAF using BTA (Botox) and LSS (LIS)



D. Recurrence rate in the treatment of CAF using BTA (Botox) and LSS (LIS)

Figure 3. *Comparison of botulinum toxin type A and lateral subcutaneous sphincterotomy in the treatment of chronic anal fissure*

DISCUSSION

The effectiveness and safety of lateral subcutaneous sphincterotomy and the use of botulinum toxin type A in the treatment of chronic anal fissure were analyzed. Complications after the use of BTA and LSS in the publications included in the meta-analysis were represented by acute urinary retention, wound infection, and bleeding, including ecchymoses and hematomas.

According to the results of the study, we did not get a statistically significant difference in the rate of postoperative complications after the use of the studied methods of treatment.

However, some authors point to a higher safety of botulinum toxin type A injections in comparison with sphincterotomy [25].

Postoperative anal incontinence, as the most dangerous complication, was analyzed separately.

According to the data obtained, the risk of postoperative AI after the use of BTA is 0.86 times lower in the period of follow-up of patients from 4.5 to 60 months than after LSS.

The discussion regarding the effectiveness of the compared methods of treatment of CAF and the rate of anal incontinence after their use remains open.

So, Garg P. et al. after analyzing the results of 22 randomized clinical trials, found that the overall rate of AI development after performing lateral subcutaneous sphincterotomy was 14% [26].

In turn, Nelson R. et al. conducted two separate meta-analyses evaluating conservative and surgical treatment of anal fissures, which did not reveal a significant difference in the rate of anal incontinence in patients after 3 years of follow-up [19,27].

In 2017, Ebinger S. M. et al. conducted the first network meta-analysis dedicated to the treatment of CAF, according to the results of which the rate of epithelization after LSS was 93.1% with a failure rate of 9.4%, and after BTA injections – 62.6% with a rate of AI-4.1% with follow-up periods of 2 weeks to 5 years [28].

When comparing the studied treatment methods, it was found that the use of botulinum toxin type A reduces the risk of developing postoperative AI, but is inferior to lateral sphincterotomy in the effectiveness of treatment and the recurrence rate of the disease [22,29-34].

The above results coincide with the data of other researchers [28,35,36] and may be associated with a temporary reversible effect of BTA in contrast to permanent and persistent relaxation of the internal sphincter after LSS performance.

The use of botulinum toxin type A compared with other conservative methods in the treatment of CAF (lidocain, nitroglycerin and diltiazem ointments), is accompanied by lesser recurrence rate and the occurrence of side effects and complications of equal or greater efficiency, which is confirmed by several authors [37-45].

In the analyzed studies, various techniques of BTA application were used (the dose and dilution of the drug in saline solution, the points of administration, the method of anesthesia used) [22,29-34]. Bobkiewicz A. et al., after analyzing 34 studies and 1,577 patients in their meta-analysis, concluded that the effectiveness of BTA, the rate of postoperative AI and other complications after its use do not depend on the dose of the drug administered [25].

In the meta-analysis by Lin J.X. et al. including 18 studies and 1,158 patients, the authors tried to determine the optimal dose and points of administration of botulinum toxin type A, but when comparing different methods of using BTA, they also did not get statistically significant differences, but concluded that further studies with longer follow-up periods were necessary [46].

It is worth noting that in all the meta-analysis studies, botulinum toxin type A was used in isolation, which may affect the effectiveness of treatment of patients with CAF.

We share the point of view of a number of authors, according to whom the injection of BTA in combination with the fissure excision will have an advantage over its isolated application [28,44].

CONCLUSION

As a result of the systematic review and meta-analysis, it was found that the compared methods can not be the «gold» standard in the treatment of chronic anal fissure.

Despite the high rate of CAF epithelization after lateral subcutaneous sphincterotomy, data on the development of incontinence in the postoperative period are contradictory.

The conducted meta-analysis indicates that there is no risk of developing postoperative anal incontinence using botulinum toxin type A, but the rate of epithelization of chronic anal fissures after injection of the drug does not correspond to the level of the «gold» standard.

Studies have a pronounced variability in the dosage of BTA, the choice of injection points of the drug in the internal sphincter, which indicates the absence of developed recommendations for the use of this method of treatment of chronic anal fissure.

The unsatisfactory quality of studies, their heterogeneity, the high risk of bias in the results of publications, the lack of multicenter randomized clinical tri-

als, dictates the need to conduct a study on the comparison of fissure excision in combination with lateral subcutaneous sphincterotomy and fissure excision in combination with botulinum toxin type A injection into the internal anal sphincter.

PARTICIPATION OF THE AUTHORS

Concept and design of the study: *Chrukin R.Yu., Zharkov E.E., Nagudov M.A.*

Collection and processing of the material: *Khryukin R.Yu., Zharkov, E.E., Nagudov M.A., Arslanbekova K.I.*

Statistical processing: *Khryukin R.Yu., Nagudov M.A., Zharkov E.E.*

Writing the text: *Khryukin R.Yu., Zharkov E.E.*

Editing: *Kostarev I.V., Zharkov E.E.*

THE AUTHORS DECLARE NO CONFLICTS OF INTEREST

REFERENCES:

1. Stewart DBSr, Gaertner W, Glasgow S. Clinical practice guideline for the management of anal fissures. *Dis Colon Rectum.* 2017;60 (1):7-14.
2. Motie MR, Hashemi P. Chronic anal fissure: a comparative study of medical treatment versus surgical sphincterotomy. *Acta Med Iran.* 2016;54 (7):437-440.
3. Adamova Z, Slovacek R, Bar T. Anal fissure. *Cas Lek Cesk.* 2015;154 (1):11-13.
4. Malaty HM, Sansgiry S, Artinyan A. Time Trends, clinical characteristics, and risk factors of chronic anal fissure among a national cohort of patients with inflammatory bowel disease. *Dig Dis Sci.* 2016;61 (3):861-864.
5. Shelygin Yu.A. Clinical recommendations. Coloproctology. Ed. Corresponding Member RAS Yu.A. Shelygin. M.: GEOTAR-Media, 2015, pp. 12-29. (in Russ.).
6. Shelygin Yu.A., Frolov S.A., Orlova L.P. Immediate results of a comprehensive treatment of chronic anal fissure. *Koloproktologia.* 2010; no. 1(31), pp. 4-9. (in Russ.).
7. Blagodarny L.A., Poletov N.N., Zharkov E.E. Pathogenesis of anal fissures. *Koloproktologia.* 2007; no. 1(19), pp. 38-41. (in Russ.).
8. Blagodarny L.A., Zharkov E.E. The results of conservative treatment of chronic anal fissure in combination with bleeding hemorrhoids. *Koloproktologia.* 2007; no. 1(19), pp. 34-38. (in Russ.).
9. 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.).
10. 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.).
11. Kuypers HC. Is there really sphincter spasm in anal fissure? *Dis Colon Rectum.* 1983;8 (26):493-494.
12. Lund JN, Binch C, McGrath J. Topographical distribution of blood supply to the anal canal. *Br J Surg.* 1999;4 (86):496-498.
13. Lund JN, Scholefield JH. Internal sphincter spasm in anal fissure. *Br J Surg.* 1997;12 (84): 1723-1724.
14. Schouten WR, Briel JW, Auwerda JJ. Anal fissure: new concepts in pathogenesis and treatment. *Scand J Gastroenterol Suppl.* 1996;218:78-81.
15. Schouten WR, Briel JW, Auwerda JJ. Ischaemic nature of anal fissure. *Br J Surg.* 1996;1 (83):63-65.
16. Schouten WR, Briel JW, Auwerda JJ. Relationship between anal pressure and anodermal blood flow. The vascular pathogenesis of anal fissures. *Dis Colon Rectum.* 1994;7 (37):664-669.
17. Notaras MJ. Lateral subcutaneous sphincterotomy for anal fissure – a new technique. *Proc R Soc Med.* 1969;62 (7):713.
18. Eisenhammer S. The evaluation of the internal anal sphincterotomy operation with special reference to anal fissure. *Surg Gynecol Obstet.* 1959;109:583-590.
19. Nelson R. Non surgical therapy for anal fissure. *Cochrane Database Syst Rev.* 2006 (4): CD003431.
20. Davies I, Dafydd L, Davies L. Long term outcomes after lateral anal sphincterotomy for anal fissure: a retrospective cohort study. *Surg Today.* 2014;44 (6):1032-1039.
21. Lysy J, Israelit-Yatzkan Y, Sestiery-Ittah M. Topical nitrates potentiate the effect of botulinum toxin in the treatment of patients with refractory anal fissure. *Gut.* 2001;48:221-224.
22. Massoud BW, Mehrdad V, Baharak T. Botulinum toxin injection versus internal anal sphincterotomy for the treatment of chronic anal fissure. *Ann Saudi Med.* 2005;25:140-142.
23. Liberati A, Altman D, Tetzlaff J. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate healthcare interventions: explanation and elaboration. *BMJ (Clinical research ed.).* 2009;(339),p. b2700.
24. Higgins JP, Altman DP, Gøtzsche PC. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. *Br. Med. J.* 2011;343:889-893.
25. Bobkiewicz A, Francuzik W, Krokowicz L. Botulinum Toxin Injection for Treatment of Chronic Anal Fissure: Is There Any Dose-Dependent Efficiency? A Meta-Analysis. *World J Surg.* 2016;40 (12):3064-3072. doi: 10.1007/s00268-016-3693-9.
26. Garg P, Garg M, Menon GR. Long-term continence disturbance after lateral internal sphincterotomy for chronic anal fissure: a systematic review and meta-analysis. *Colorectal Dis.* 2013;15 (3):104-117. doi: 10.1111/codi.12108.
27. Nelson RL, Chattopadhyay A, Brooks W. Operative procedures for fissure in ano. *Cochrane Database Syst Rev.* 2011: CD002199.
28. Ebinger SM, Hardt J, Warschkow R. Operative and medical treatment of chronic anal fissures-a review and network meta-analysis of randomized controlled trials. *J Gastroenterol.* 2017;52 (6):663-676. doi: 10.1007/s00535-017-1335-0.
29. Mentes BB, Irkorucu O, Akin M. Comparison of botulinum toxin injection and lateral internal sphincterotomy for the treatment of chronic anal fissure. *Dis Colon Rectum.* 2003;46 (2):232-237.
30. Arroyo A, Perez F, Serrano P. Surgical versus chemical (botulinum toxin) sphincterotomy for chronic anal fissure: long-term results of a prospective randomized clinical and manometric study. *Am J Surg.* 2005;189 (4):429-434.
31. Iswariah H, Stephens J, Rieger N. Randomized prospective controlled trial of lateral internal sphincterotomy versus injection of botulinum toxin for the treatment of idiopathic fissure in ano. *ANZ J Surg.* 2005;75 (7):553-555.
32. Abd Elhady HM, Othman IH, Hablus MA. Long-term prospective randomised clinical and manometric comparison between surgical and chemical sphincterotomy for treatment of chronic anal fissure. *S Afr J Surg.* 2009;47 (4):112-114.
33. 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):2730-2734.
34. Valizadeh N, Jalaly NY, Hassanzadeh M. Botulinum toxin injection versus lateral internal sphincterotomy for the treatment of

chronic anal fissure: randomized prospective controlled trial. *Langenbecks Arch Surg*. 2012;397 (7):1093-1098.
35. Shao WJ, Li GC, Zhang ZK. Systematic review and meta-analysis of randomized controlled trials comparing botulinum toxin injection with lateral internal sphincterotomy for chronic anal fissure. *Int J Colorectal Dis*. 2009;24:995-1000.
36. Sajid MS, Hunte S, Hippolyte S. Comparison of surgical vs chemical sphincterotomy using botulinum toxin for the treatment of chronic anal fissure: a meta-analysis. *Colorectal Dis*. 2008;10:547-552.
37. Colak T, Ipek T, Kanik A. A randomized trial of botulinum toxin vs. lidocaine pomade for chronic anal fissure. *Acta Gastroenterol Belg*. 2002;65:187-190.
38. Brisinda G, Cadeddu F, Brandara F. Randomized clinical trial comparing botulinum toxin injections with 0.2% nitroglycerin ointment for chronic anal fissure. *Br J Surg*. 2007;94:162-167.
39. Brisinda G, Maria G, Bentivoglio AR. A comparison of injections of botulinum toxin and topical nitroglycerin ointment for the treatment of chronic anal fissure. *N Engl J Med*. 1999;341:65-69.
40. Richard CS, Gregoire R, Plewes EA. 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;43:1048-1057.
41. Jonas M, Neal KR, Abercrombie JF. A randomized trial of oral vs. topical diltiazem for chronic anal fissures. *Dis Colon Rectum*. 2001;44:1074-1078.
42. Jones OM, Brading AF, Mortensen NJ. The mechanism of action of botulinum toxin on the internal anal sphincter. *Colorect Dis*. 2002;4(1):71-72.
43. Bhardwaj R, Drye E, Vaizey C. Novel delivery of botulinum toxin for the treatment of anal fissures. *Colorect Dis*. 2006;8:360-364.
44. Lindsey I, Cunningham C, Jones OM. Fissurectomy – botulinum toxin: a novel sphincter-sparing procedure for medically resistant chronic anal fissure. *Dis Colon Rectum*. 2004;47:1947-1952.
45. Samim M, Twigt B, Stoker L. Topical diltiazem cream versus botulinum toxin a for the treatment of chronic anal fissure: a double-blind randomized clinical trial. *An Surg*. 2012;255(1):18-22. doi: 10.1097/SLA.0b013e318225178a.
46. Lin JX, Krishna S, Su'a B. Optimal Dosing of Botulinum Toxin for Treatment of Chronic Anal Fissure: A Systematic Review and Meta-Analysis. *Dis Colon Rectum*. 2016;59 (9):886-894. doi: 10.1097/DCR.0000000000000612.

Received – 10.01.2020 *Revised – 26.03.2020* *Accepted for publication – 11.05.2020*