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Modern Therapeutic Approaches to the Treatment of Anal Fissure

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ABSTRACT

Anal fissure (AF) is one of the most common coloproctological diseases which causes reduction in quality of life. The incidence of anal fissure is 2,1 - 2,3% or 21-23 cases per 1000 working-age people in Russian Federation. Fissures occur most frequently in the posterior midline of the anal canal and associated with the poor blood supply to this area. In some cases, AFs are seen in the anterior midline and rarely seen laterally in the anal. The exact etiology of anal fissures is not entirely clear. However, there is a clear association with the increased pressure within the anal canal. Anal fissures may be acute and chronic. Up to 87% of AFs are resolved with conservative management which includes sitz baths, laxatives, increased intake of fluid and fiber. Patients with chronic anal fissures require the addition of medical treatment. First line therapy includes application of calcium channel blockers (CCB) or topical nitrates in addition to increasing dietary fiber. Medical management is usually effective in 65-95%. However, the range of worldwide approved drugs containing CCBs or nitrates is still very poor. If fissures do not resolve after 6-8 weeks of first line therapy, referral to secondary care (botulinum toxin injections and surgical sphincterotomy) is made. The healing rate in case lateral internal sphincterotomy is close to 100%, however, the fecal incontinence rate ranges from 8% to 30%. In this regard, the development of new effective drugs with the minimum side effects is still a critical task.

Keywords: anal fissure, botulinum toxin, calcium channel blockers, internal sphincter spasm, topical nitrates.

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INTRODUCTION

Anal fissure is a linear or ellipsoidal defect of the anal canal mucous membrane with the length of 2-2.5 cm, starting below the dentate line and ending at the anal verge. [1] The disease was first described in 1934 by Lockhart-Mummery [1]. To date, AF is considered as one of the most common coloproctological diseases. According to literature data, the incidence of anal fissure is 0.11% or 1.1 cases per 1000 people in the United States and 0.29% or 2.9 per 1000 people in the European Union[2,3]. It accounts for 11-15 % of all colon diseases, and the incidence ranges from 20 to 23 per 1,000 or 2.0 – 2.3% of working-age population in Russian Federation[4]. According to Douglas W Mapel et al., 342,000 anal fissures are diagnosed annually in the USA, which is comparable to the number of annually performed appendectomies[2].

Anal fissures are classified into initial and secondary. The initial lesions are caused by overstretching of anal canal. Secondary AFs may occur as the result of inflammatory, dermatologic, infectious, venereal or neoplastic disease. AFs can also be divided into acute (AAF) (lasting less than 6 weeks) or chronic (CAF) (lasting more than 6 weeks). AAF is associated with anal pain and/or bleeding with defecation and CAF is characterized by a skin tag or sentinel pile distally, hypertrophied anal papilla and exposed fibers of internal anal sphincters at the base [5]. Approximately 40% of patients with AAF progress to having CAF[6,7].

Etiology of anal fissure is not entirely clear. Many theories have been advanced to explain the origin of AF but trauma of faecal mass and hypertonicity of the internal sphincter are considered as the most important factors. Other factors include infections, anatomical configuration of the sphincter muscles and blood supply to the mucosa of the anal canal[8]. Local ischemia caused by spasm of internal anal sphincter (IAS) results in poor healing and, consequently, leads to persisting anal fissure[9]. The main goal of anal fissure management is to break the cycle of IAS spasm allowing improved blood flow to the AF so that healing can occur. Modern approaches to the treatment of AF include conservative measures, chemical and surgical sphincterotomy.

CONSERVATIVE TREATMENT OF ACUTE ANAL FISSURE

Treatment of anal fissure involves several approaches and is determined by its type (acute/chronic). Thus, for AAF the standard scheme of conservative treatment includes sitz baths and laxatives. In addition, the American Society of Colon and Rectal Surgeons (ASCRS) recommends patients to increase intake of fluid and fiber[3]. The goal for adults is to consume 25–30 g of fiber daily [10]. ASCRS also states that conservative therapy should always be the first step in therapy for all fissure types because it is safe and has few side effects. This approach showed symptomatic improvement and faster healing of the AF in comparison with the use of 2% lidocaine ointment and 2% hydrocortisone cream in the randomized controlled clinical trial [11].Application of the abovementioned therapeutic approaches allow to relieve pain syndrome, to achieve bleeding control and healing in 50% of patients with acute anal fissures with minimal side effects.

In the presence of internal sphincter spasm, and therefore the transition of anal fissure to chronic, it is recommended to include medicinal, operative and integrated methods in the therapy.

THERAPEUTIC APPROACHES TO THE TREATMENT OF ANAL FISSURE

Drugs of different pharmacological groups are used on the basis of knowledge about key substances involved in the regulation of IAS tone. Methods of "chemical sphincterotomy" have been known since the 90s of the 20th century and include application of topical nitrates, calcium channel blockers (CCB), botulinum toxin injections, etc. [12,13]. Some of the most commonly used drugs approved in Russian Federation are summarized in Table 1:

Table 1: Some drugs for the treatment of anal fissure approved in Russian Federation.

№	Trade name, manufacturer	Pharmacotherapeutic group* of the drug	Dosage form	Active pharmaceutical ingredient(s)
1.	"Fissario", NovaMedica, LLC (Russia)	Drugs for the treatment of haemorrhoids	Gel for rectal and topical application	Nifedipine Lidocaine hydrochloride
	"Relief® Ultra", Instituto De Angeli S.R.L. (Italy)		Suppository	Hydrocortisone 21-acetate Zinc Sulfate monohydrate
	"Proctosan®", STADA Arzneimittel AG (Germany)		Rectal ointment Suppository	Bufexamac Bismuth subgallate Titanium dioxide Lidocaine hydrochloride monohydrate
	"Relief®", Instituto De Angeli S.R.L. (Italy)		Rectal ointment Suppository	Phenylephrine hydrochloride
	"Posterisan®", DR. KADE Pharmazeutische Fabrik GmbH (Germany)		Rectal ointment Suppository	Bacterial cultural suspension
2.	"Bisacodyl", Tula pharmaceutical factory, LLC (Russia)	Laxatives	Tablets Suppository	Bisacodyl
	"Dulcolax®", Delpharm Reims (France)		Suppository	Bisacodyl
	"Guttalax®", Delpharm Reims (France)		Tablets Oral drops	Sodium picosulphate
	"Senade", Cipla LTD (India)		Tablets	Sennosides A & B
3.	"Natalsid", Nizhpharm OJSC (Russia)	Hemostatic drugs	Suppository	Sodium alginate
4.	"Aurobin", Gedeon Richter Plc. (Hungary)	Glucocorticosteroids + antimicrobial agents	Ointment for topical and rectal application	Prednisolone caproate Lidocaine hydrochloride Dexpanthenol

*according to State Register of Medicines of the Russian Federation (https://grls.rosminzdrav.ru/GRLS.aspx)

Clinical Practice Guideline for the Management of Anal Fissures of the American Society of Colon and Rectal surgeons recommends to use topical nitrates or calcium channel blockers as the first line therapy. However, Table 1 shows that currently only one drug having CCB (nifedipine) in the composition has been approved by the Ministry of Health of Russian Federation so far. Regarding to topical nitrates, there are still no drugs available on Russian market. Their effectiveness was proved in clinical trials, so it is important to consider this group of substances in details.

Topical nitrates

First-line preparations include organic nitrates. Among them, 1% nitroglycerin ointment, preparations of isosorbide dinitrate can be distinguished. The metabolism of these substances leads to release of nitrogen oxide (NO), identical to the endothelial relaxing factor. NO was reported to be the neurotransmitter mediating relaxation of the IAS muscle in 1990's. As a consequence, in 1997 it was found out that topical application of 0.2% glyceryl trinitrate ointment (GTN) result in relaxation of the IAS by manometric studies[14]. Treatment with the preparations containing nitrates has shown healing in approximately two-thirds of patients. In addition, meta-analysis of randomized trials demonstrated a significantly better result in comparison with placebo treatment[15].Nowadays several drugs having nitrates as an active pharmaceutical ingredient are marketed. For example, topical glyceryl trinitrate 0.2% ointment (Rectogesic®) which was approved in 2004 by U.K.'s Medicines and Healthcare Products Regulatory Agency for the topical treatment of pain associated with CAF[16]. One more preparation is 0,4% nitroglycerin ointment RECTIV® which was approved by FDA in 2011 and it is the only marketed topical preparation for the treatment of anal fissures in the USA[17]. Among the side effects of organic nitrates are the severe headaches that were noted by Brisinda and colleagues in a clinical study comparing local use of nitrates and botulinum toxin injections[18]. It is worth noting that the effect is dose-dependent and, according to Beaty et al., causes therapy interruption in 20% of patients. In

addition, the use of nitroglycerin drugs causes burning in the anal canal[1]. However, A. Christie and J.F. Guest showed in their study that initial use of 0.2% glyceryl trinitrate compared to lateral internal sphincterotomy (LIS) in the treatment of a CAF potentially reduces direct healthcare costs without any loss in effectiveness[19].

Botulinum toxin

Injections of botulinum toxin (BT) are also used in order to eliminate spasm of IAS. Botulinum toxin is an exotoxin produced by *Clostridium botulinum* bacteria. Botulinum toxin injections were first used for the treatment of anal fissure by Jost and Schimrigk in 1993. The mechanism of action in improving CAF and spasm is likely mainly due to cholinergic nerve terminal blockade, preventing spasm, as well as blockade of the post-ganglionic sympathetic fibers, preventing sweating, and subsequent fissuring. Beneficial effects have been shown to last from 4 months to 1 year. [20]. Among marketed preparations of BT, Dysport® and BOTOX® are usually used. A study conducted by Brisinda with colleagues showed a higher efficacy of botulinum toxin injections compared to the local use of organic nitrates [18]. Among the frequent side effects of botulinum toxin can be distinguished incontinence, increased gas formation in the intestine [21–25]. In addition, injection of the drug involves the assistance of qualified medical personnel, which also complicates the use of botulinum toxin.

Calcium channel blockers.

Tone of the IAS is regulated by four mechanisms: three of them involve membrane potential, L-type Ca^{2+} channels and electromechanical coupling (i.e, summation of asynchronous phasic activity, partial tetanus, and window current), whereas the fourth involves the regulation of myofilament Ca2+ sensitivity [26]. In connection with this, calcium channel blockers (CCB) are one of the promising and practically significant group of substances for the treatment of anal fissure.

Calcium channel L-type blockers are divided into dihydropyridine and non-dihydropyridine by their chemical structure. The representative of nonhydropyridine CCB is diltiazem. A large number of dosage forms were developed on the basis of it. Among them is 2% "Diltiazem" gel. Healing of AF is achieved in approximately 60-70% cases [27,28]. It is worth noting that the therapy with this drug, and in general with the drugs of the CCB group, is accompanied by a low incidence of side effects.

Dihydropyridine CCB of L-type include nifedipine, felodipine, amlodipine, etc. Unlike non-dihydropyridine derivatives, they selectively block calcium channels in blood vessels, do not slow down AV-conduction, to a lesser extent reduce cardiac muscle contractile ability[29,30].

In addition to the chemical classification of CCB, it is also accepted to classify them by generations. According to this classification diltiazem belongs to the first generation along with dihydropyridine CCB— nifedipine. On the basis of nifedipine there were developed such dosage forms for the treatment of anal fissures, as: 0.5% ointment [31], 0.2 -0.5% gel [32] ,0,5% cream [33]. The effectiveness of these formulations is comparable with sphincterotomy[28,31]. In addition, formulations with nifedipine showed fewer side effects than botulinum toxin and organic nitrates in clinical trials[34]. New drug "Fissario" containing nifedipine and lidocaine hydrochloride in the form of gel was approved in Russia in 2018. There are no approved topical drugs having CCB as API in the USA or EU. However, in the US compounding pharmacies can make a topical gel from an oral formulation (typical doses: diltiazem 2%; nifedipine 0,2 – 0,5%)[35]. According to studies, "Fissario" showed significantly better efficacy profile in comparison with "Relif advance" containing benzocaine[36].

The second generation CCBs includes the following medicinal substances of the nifedipine group: felodipine, nicardipine, nitrendipine, etc. Unlike the first generation of CCBs, these substances have a longer duration of action, higher tissue specificity and fewer side effects. Felodipine, for example, is more selective to vessels in comparison with nifedipine[37].

The mechanism of CCBs acting on L-type channels is the violation of the intake of calcium ions inside the smooth muscle cell. It is presented in detail in Figure 1.

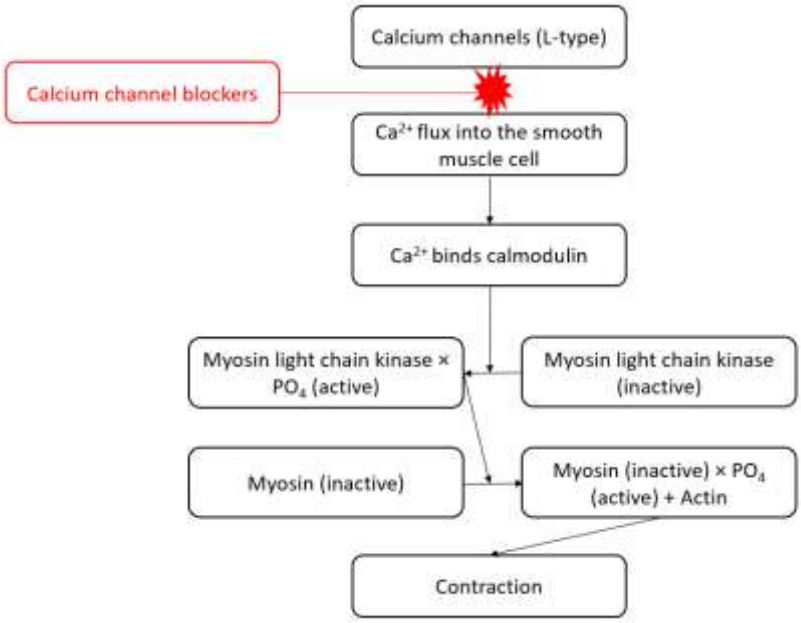

Figure 1: Mechanism of action of calcium channel blockers in smooth muscles.

Blocking of the smooth muscle cell contraction process leads to vasodilatation and relaxation of the anal sphincter. Thus, blood flow to the affected area increases, which has a beneficial effect on the healing process of anal fissure[5].

OTHER APPROACHES

The tonus of IAS smooth muscle is determined, on the one hand, by the properties of smooth muscle fibers. On the other hand, the nervous system also plays a role in influencing the tone of the IAS [31]. In this regard, it is worth noting the active pharmaceutical ingredient (API) Bethanechol which belongs to the group of prokinetics and stimulates M-choline receptors. Based on it, there was developed a 0,1% gel formulation. However, comparative clinical studies of bethanechol and diltiazem gels have shown that bethanechol is not the most effective treatment for anal fissures. According to data, after eight weeks, only 50-67% of patients had a fissure healing [38].

L-arginine, physiological precursor of nitric oxide, may also have a potential role in the topical treatment of chronical anal fissures. Though, further investigations are required [39].

Compositions based on extracts of natural origin are quite common. For example, Levorag® Emulgel has been developed in Italy. It includes *Hibiscus esculentus* extract containing myoxinol, which improves tissue elasticity and reduces the tone of anal sphincter [40]. Comparative clinical study demonstrated statistical noninferiority of Levorag® Emulgel compared with 2% diltiazem gel in the management CAF. The healing rate in both groups of patients was about 50% [41]. Elwakeel at al also reported about the significant beneficial effect of 1% clove oil cream against traditional treatment with stool softeners and 5% lignocaine cream in the comparative clinical trial[42].

In the event that "chemical sphincterotomy" is ineffective, surgical methods of treatment are applied, which include surgical sphincterotomy, stretching anal sphincter, anocutaneous flap, anoplasty and fissurectomy [43].

CONCLUSION

Anal fissure is a common disorder which can be effectively treated with conservative measures at its acute stage. However, chronic anal fissures require additional treatment which include application of topical nitrates and calcium channel blockers. If the fissure fails to heal, injections of botulinum toxin as well as operative management can be recommended.

The efficacy of surgical methods is close to 100% [31]. However, according to Ebinger et al, surgical treatments lead to stool incontinence in 44% of cases and worsen the quality of life of patients. In this regard, the development of modern formulations having the same or better efficacy profile but less side effects remains actual task.

CONTRIBUTION OF THE AUTHORS

All authors participated in the collection of information, its analysis, discussion and writing the text of the article.

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CONFLICT OF INTERESTS

The authors declare no conflict of interest

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