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THE VALUE OF INJECTION THERAPY WITH BOTULINUM TOXIN IN PAIN TREATMENT OF PRIMARY CHRONIC ANAL FISSURES COMPARED TO ANAL DILATION, AND LOCAL NIFEDIPINE IN COMBINATION WITH LIDOCAINE

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ABSTRACT

Introduction: Anal fissure is a longitudinal tear of the mucosa of the anal canal extending from the outer anal orifice in the direction of the dentate line of the inner anal opening. Fissures are divided into primary and secondary, and acute or chronic. Besides minimal rectal bleeding, itching and soiling, primary chronic anal fissures (PCAF) manifest with anal pain as theirs main determinant. It is described as the most troubling symptom.

Aim: To compare the effect of injection therapy with botulinum toxin A (ITBT) vs. anal dilation (AD), and local nifedipine with lidocaine (LNL) in pain treatment of PCAF.

Materials and Methods: This controlled retrospective prospective longitudinal study covered 94 patients, divided in 3 groups. The first was treated with ITBT, the second with AD and third using LNL (31, 33 and 30 patients respectively). Clostridium botulinum toxin A was used, dissolved with saline to concentration of 200 U/ml. The solution was applied to both sides of PCAF at dose of 40U. Modified technique of AD was done using 3 fingers of a single hand, progressively introduced into the anal canal, followed by gradual lateral distraction during 1 min. LNL therapy was conducted using nifedipine (0.3%) with lidocaine (1.5%) ointment, applied twice daily for 3 weeks. To measure pain, a visual analog scale (VAS) was used. The follow-up period was 12 weeks with checkup at week 4.

Results: The median age of participants was 46.6±13.9 years (50 males vs. 44 females). The type of therapy had a significantly different effect on pain at week 4 ($p=0.0003$). Severe pain was present in only 2 ITBT patients, 16 AD, and 6 LNL patients. Post hoc analyses showed different pain disappearance time by week 12 ($p <0.0001$). The mean time was shortest in ITBT group (6.1±1.5 weeks). Anal pain intensity significantly differed among the 3 groups (Fisher exact, $p=0.002$). Namely, 71% in ITBT group rated the pain as weakest (VAS score 1) compared to 18.2% in AD and 30% of patients in LNL group. The overall pain reduction significance was in favor of ITBT, due to the differences between the ITBT and AD groups ($p=0.00024$) and ITBT compared to LNL group ($p=0.018$).

Conclusion: ITBT is superior to AD and LNL in reducing pain in PCAF.

Keywords: Primary chronic anal fissures, anal pain, injection therapy with botulinum toxin A, anal dilation, local nifedipine in combination with lidocaine

INTRODUCTION

Described for the first time by British surgeon John Percy in 1934, anal fissures are divided into primary and secondary, and acute or chronic. Primary anal fissures do not appear as part of any other disease or condition. Most anal fissures are primary and a consequence of local trauma, such as passage of hard stool, diarrhea, vaginal delivery, or anal intercourse. The secondary anal fissures are large and irregular, multiple, and found in patients with inflammatory bowel diseases, tuberculosis, anal carcinoma, and some sexually transmitted diseases [1].

Primary chronic anal fissures manifest with anal pain. It is described as the most troubling one. Although bright red blood per rectum or minimal rectal bleeding, soiling and itching are possible, pain is still a crucial symptom. Anal pain is the cornerstone of any suspicion of the presence of PCAF and may be present not only during defecation but also for hours afterwards. It is the main determinant of the time frame definition of PCAF. Monitoring patients with PCAF is necessary in order to have insight, not only into the process of healing, eventual persistence or repeated occurrence, but also in the improvement of symptoms. The common goals of all forms of therapy are to eliminate the symptoms of bleeding, pruritus, soiling, but most of all pain, thereby achieving healing. In this study we aimed to compare the effect of injection therapy with botulinum toxin A vs. anal dilation, and local nifedipine with lidocaine in treatment of pain in primary chronic anal fissures.

MATERIALS AND METHODS

BIn a controlled retrospective prospective longitudinal study conducted over the period of three years, a total of 94 patients, divided into 3 groups, were treated on ambulatory base at the University Clinic of Gasteroenterohepatology in Skopje. All the patients underwent a previous colonoscopy with the exact description of the position of PCAF and its morphological features. The duration of anal pain of minimum 6 weeks prior to intervention was used as the inclusion criterion. The presence of acute anal fissure, inflammatory bowel disease, active local or systemic malignant disease, tuberculosis or sarcoidosis, perianal fistulas and abscesses, planned or present pregnancy, parallel therapy with oral calcium channel blockers, present local infection, ongoing chemotherapy, previous surgery in the anal area, and presence of a third or fourth degree hemorrhoids, were used as exclusion criteria.

The first group was treated with ITBT, the second with AD and third using LNL (31, 33 and 30 patients, respectively). Improvement of the anal pain during defecation and thereafter was defined by its decrease or disappearance and was used as a measure of effectiveness.

ITBT was performed using Clostridium botulinum A toxin - a hemagglutination complex (Dysport®, Ipsen Biopharm Ltd, Wrexham, United Kingdom) in the form of a powder for the injection solution. This was packaged in vial with a volume of 3 ml containing 500 units (U) botulinum toxin A, previously placed and stored at 2-8 ºC, and then dissolved with a sterile saline solution in an amount of 2.5 ml, giving a final concentration of 200 U/ml. The solution was injected to both sides of PCAF in the internal anal sphincter (IAS) at a total dose of 40U, using 1 ml syringe and a needle of 10 mm, 25 G. (Figure 1).

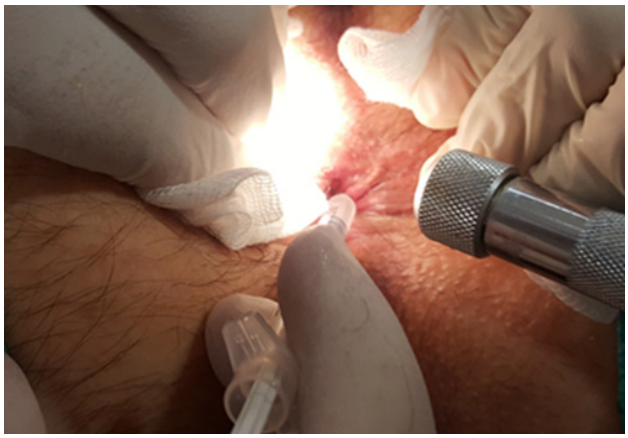


Figure 1. *Injection therapy with Clostridium botulinum toxin A solution*

A modified technique of AD was carried out with the initial insertion of the anoscope (Hirschmann 65 mm). After its extraction, 3 fingers of a single hand were gradually and progressively introduced into the anal canal, followed by gradual lateral distraction of the IAS, acting only in the direction towards 3 and 9 o'clock (Figure 2). The duration of AD was shortened compared to Lord's technique and lasted for 1 minute. The idea to change the traditional technique of AD,

in terms of mode of execution and its shortened duration, was a result of intending to minimize the intensity and extent of the strength by applying fingers only from one hand, thus avoiding the risk of side effects.

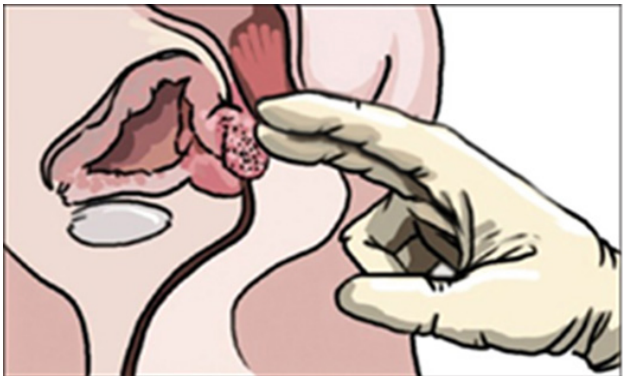


Figure 2. *Modified anal dilation technique using one arm*

LNL therapy was conducted using nifedipine (0.3%) with lidocaine (1.5%) ointment, applied twice daily for 3 weeks, in the anal canal at a depth of about 1 cm using endorectal applicator and perianally in a total amount of 2.5-3g. All the patients were especially advised that a high level of adherence is necessary.

None of the patients within the groups received any other additional form of therapy, nor was transition from one to another form of therapy allowed. The pain severity was recorded as mild, moderate, and severe using the VAS and in absolute values using VAS score. The follow-up period was 12 weeks with the first checkup at week 4. The measures of effectiveness were improvement with reduction or absence of pain, and healing of the fissure was defined as its complete epithelization. By contrast, the need for surgery was considered a treatment failure.

The study protocol and informed consent were submitted for consideration and approved by the Ethics Committee of the Faculty of Medicine at Ss. Cyril and Methodius University in Skopje. The collected data were processed using the statistical program SPSS 20 for Windows.

RESULTS

Through the total of 94 patients, 53.2% were male and 46.8% female, with a median age of 46.6 ± 13.9 years in the range of 20-75 years. The tested differences in the distribution of males and females among the three groups were statistically non-significant (p = 0.79), and the average age of patients in the three groups was similar (p=0.99), thus making the groups homogeneous in relation to the sex and age.

The pain duration differences before intervention between three groups were confirmed as insignificant (p = 0.94) [Table 1].

Treatment failure with need for surgical intervention was significantly influenced by the duration of pain before the start of treatment in all groups of patients. The mean duration of pain was significantly longer in patients that were referred for lateral internal sphincterotomy (Table 2).

Table 1. *Pain duration before intervention*

Type of intervention	Prior intervention: Descriptive Statistics (Pain duration in weeks)				p value
	N	mean ± SD	median	IQR	
Group 1	31	23.81 ± 20.2	16	10 – 32	H=0.111 p=0.94 ns
Group 2	33	23.48 ± 20.8	16	12 – 28	
Group 3	30	35.60 ± 85.1	19	10 – 28	

H (Kruskal-Wallis test)

Table 2. *Pain duration before intervention in treatment failures with need for surgery*

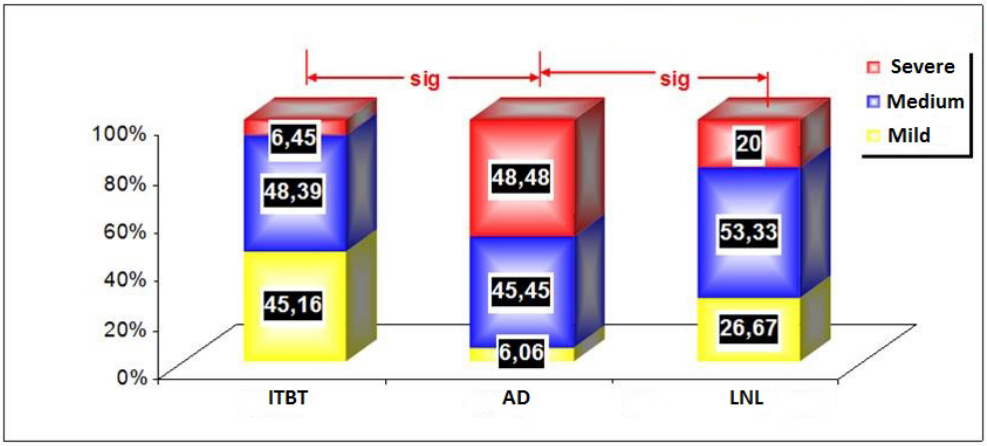
Type of intervention	Treatment failure	Descriptive Statistics (Pain duration in weeks)				p value
		N	mean ± SD	median	(IQR)	
Group 1	Yes	8	45.37 ± 27.9	44	25 – 60	Z=2.95 p=0.003 sig
	No	23	16.30 ± 9.1	14	9 – 18	
Group 2	Yes	7	39.71 ± 25.7	36	14 – 60	Z=2.4 p=0.015 sig
	No	26	19.11 ± 17.4	13	10 – 24	
Group 3	Yes	13	56.46 ± 127.9	20	10 – 28	Z=2.88 p=0.038 sig
	No	17	19.65 ± 14.8	12	10 – 24	

Z (Mann-Whitney test)

Table 3. *Tested differences of anal pain intensity at week 4 according to VAS*

Tested differences – all groups (Chi-square=21.38 p=0.0003 sig)		
Type of intervention	**Group 2**	**Group 3**
Group 1	p=0.0000001 sig	p=0.18 ns
Group 2		p=0.02 sig

Chart 1. *Anal pain intensity at week 4 according to VAS*



Type of therapy had a significant effect on pain at week 4 (p=0.0003). A history of mild pain was registered among 45.2% (14) ITBT patients, yet only in two AD patients and 26.7% (8) in the group treated with topical nifedipine combined with lidocaine. Severe pain was present in only 2 (6.5%) ITBT patients, 16 (48.5%) AD, and 6 (20%) LNL patients (Table 3, Chart 1).

Patients who did not have pain at week 12 reported a significantly different time of pain disappearance, depending on the type of intervention ($p < 0.0001$). The mean time was shortest in ITBT group (6.1±1.5 weeks). Patients treated with AD had significantly longer duration of pain during defecation compared to patients treated with ITBT and compared to those treated with LNL. Post hoc analyses confirmed different pain disappearance time until week 12 ($p < 0.0001$) [Table 4, Chart 2].

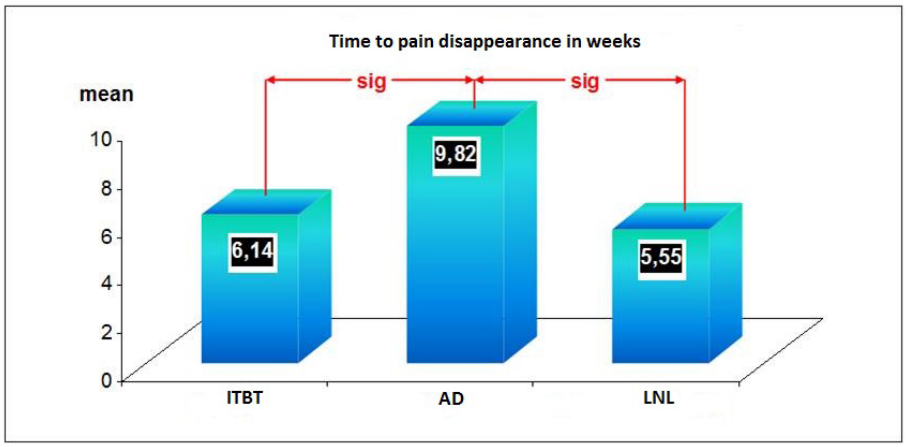
Anal pain intensity differed significantly among the 3 groups (Fisher exact, p=0.002). In

Table 4. Tested differences for pain disappearance at week 12

Tested differences – all groups F=74.64 p=0.00000 sig Post hoc Tukey test		
Type of intervention	**Group 2**	**Group 3**
Group 1	p=0.0001 sig	p=0.35 ns
Group 2		p=0.0001 sig

F (Analysis of Variance)

Chart 2. *Time to pain disappearance at week 12*



the ITBT group, 71% of patients rated the pain as weakest (VAS score 1) compared to 18.2% in AD and 30% in LNL group. The overall pain reduction significance in favor of ITBT, was due to the differences between ITBT and AD group (p=0.00024) and ITBT compared to LNL group (p=0.018) [Table 5, Chart 3].

In the analyzed period, at starting point on the day of intervention, at week 4 and 12 weeks after intervention, the pain intensity, measured as mild, medium and severe according to VAS, decreased significantly in all three groups, but the number of patients with severe pain at the end of the study was lowest (6.45%) in ITBT group (Table 6).

DISCUSSION

Anal pain is the cornerstone of any suspicion of PCAF and may be present not only during defecation but also for hours afterwards. It is actually the main determinant of the time frame definition of PCAF. There is still no clear, generally accept-

Table 5. *Tested differences of anal pain intensity at week 12*

Tested differences – all groups (Fisher exact, p=0.002 s)		
Type of intervention	**Group 2**	**Group 3**
Group 1	p=0.00024 sig	p=0.018 sig
Group 2		p=0.55 ns

Chart 3. *Differences in anal pain intensity measured by VAS score at week 12*

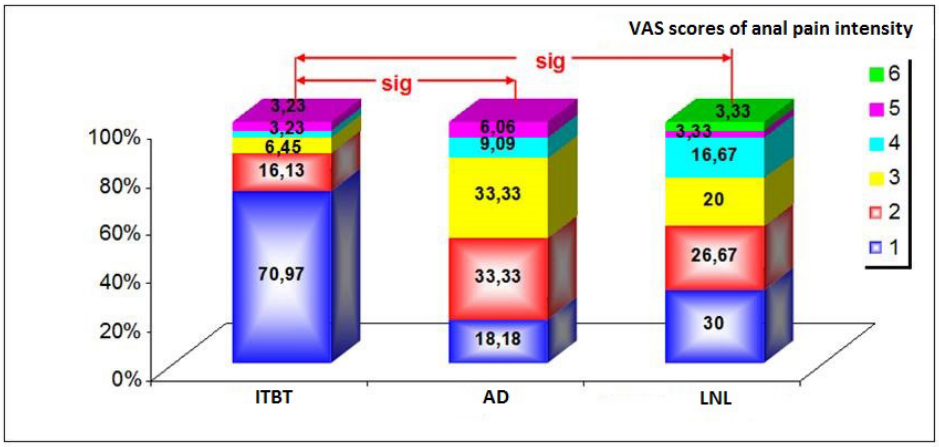


Table 6. *Intragroup differences of pain intensity according to VAS during study period*

Type of intervention	Pain intensity according to VAS	Start	Week 4	Week 12
Group 1	Mild		14 (45.16%)	29 (93.55%)
	Moderate		15 (48.39%)	2 (6.45%)
	Severe	31 (100%)	2 (6.45%)	
	Friedman ANOVA =55.9 p<0.0001 start vs. 4w p=0.000003; start vs. 12w p=0.000001; 4w vs. 12w p=0.0004			
Group 2	Mild		2 (6.06%)	28 (84.85%)
	Moderate		15 (45.45%)	5 (15.15%)
	Severe	33 (100%)	16 (48.49%)	
	Friedman ANOVA =58.7 p<0.0001 start vs. 4w p=0.00029; start vs. 12w p=0.000001; 4w vs. 12w p=0.000002			
Group 3	Mild		8 (26.67%)	23 (76.67%)
	Moderate	2 (6.67%)	16 (53.33%)	7 (23.33%)
	Severe	28 (93.33%)	6 (20%)	
	Friedman ANOVA =4997 p<0.0001 start vs. 4w p=0.00027; start vs. 12w p=0.000003; 4w vs. 12w p=0.0002			

ed global consensus on how long an anal fissure should persist and the difficulties it causes in order to be defined as chronic. Thus, according to older studies, anal fissures were defined as chronic in all cases in which morphological signs and anal pain lasted longer than 4 weeks [2]. More recent data, such as those from the penultimate ACG clinical guideline for the management of benign anorectal disorders from 2014, that were reconfirmed in its last update from 2021, show that a PCAF is defined as non-healing when lasting more than 8–12 weeks [3, 4]. But according to other publications from the period in between these last two ACG guidelines, this timeframe should be at least 6 weeks, or even shorter, but with similar episodes in the past [5]. This is in parallel to criteria used in our study, wherein all the patients included had a minimum duration of anal pain of 6 weeks prior to intervention.

The common goal of all forms of therapy, such as in conservative, minimal invasive like ITBT and surgical, is to eliminate the anal pain and spasm. This breaks the vicious cycle of spasm, pain and re-injury by relaxing the IAS and reducing its resting pressure.

Although ITBT has been used for PCAF worldwide for a long time, there are still no firm recommendations, with few exceptions from the ACG guidelines [3, 4] and it is still the subject of active debate. Furthermore, in cases where the repetition of therapy is indicated, there are no widely accepted time intervals, nor number of treatments to be applied [6]. ITBT is injected into the IAS and reduces its tone, with action beginning 2 to 3 hours after injection, and pain after its application beginning to vanish after 2 to 7 days, while reported healing rates vary from 44 to 96%. According to a study published in 2017, ITBT established itself on the coloproctology scene as a result of high rates of incontinence after surgical treatments of PCAF. Compared to them, ITBT is simpler, cheaper, minimally invasive, well tolerated, does not require anesthesia, is performed mostly in outpatient settings and without the need for long-term sick leave and absence from work. According to Barbeiro S. et al, the long-term effects, without any symptoms, during the follow-up period of 5 years is 65%, with a minimal risk of side effects and possibility of repeating the therapy if initially unsuccessful. The rate of complete rehabilitation and pain decline, according to these results, is as high as 80% [7]. In our study, pain was reduced in all three groups by the end, with the highest decrease in the ITBT group, where 71% of respondents rated the pain with VAS score 1, being significantly better than the other two groups ($p=0.002$).

In a randomized study [8], 30 patients who had previously failed to respond to the application of topical isosorbide dinitrate, were randomly divided in two groups. Group A with ITBT and subsequent application of isosorbide dinitrate topically in the form of a spray (2.5 mg three times a day) for a period of 3 months and group B treated only with ITBT. Despite the healing rate after 6 weeks was significantly higher in group A (66%) versus 20% in group B ($p = 0.025$), the mean time to pain relief was not significantly different (11.4 days in group A and 18.3 days in group B).

The present experience with ITBT fell short of this time expectation in terms of pain relief. According to our results, the mean time to pain disappearance was longer, regardless of the type of therapy, with ITBT being the shortest (6.1 ± 1.5 weeks; $p < 0.0001$).

Furthermore, it has been established that 3-25% of patients are pain-free, even when PCAF recovery is not achieved. This can last up to 3 months from application of therapy. This anti-nociceptive effect has been confirmed in other painful conditions in which ITBT is used, and it is considered to have a role in pain reduction during its use after hemorrhoidectomy [9]. In our experience, the type of therapy had a significant effect on pain at week 4 ($p=0.0003$) and further at week 12 with a respectable number of patients with pain relief after 3 months.

Although AD seemed to be abandoned, there are statements that when done correctly, this technique results in rapid pain reduction in patients with PCAF. The procedure can be performed not only with general or spinal anesthesia, but also with the use of local anesthetics. After the IAS is dilated, the passage of fecal masses is facilitated, thus affecting the symptoms, primarily by reducing pain [10].

As a proof that AD does not lose popularity, there is introduction of numerous variants of this technique in recent period that are applied with variable success, but worthy of respect. Thus, in addition to Lord's technique of digital AD, the following have also been published: endoscopic anal dilatation [11], pneumatic anal balloon dilatation [12], controlled intermittent anal dilatation [13] and others. So far, at least one meta-analysis aimed at investigating the different techniques of

AD has been published, with a search date up to March 2011 [14]. This meta-analysis included nine randomized controlled trials, with a total of 562 respondents. This despite numerous objections, points towards the popularity of AD as a therapeutic option even today. From the data presented in our trial, AD failed to express better or comparable to ITBT and LNL. At week 4 severe pain was present in 48.5% AD patients compared to only 6.5% ITBT and 20% LNL patients.

The optimal duration of topical vasodilator treatments, like those using nifedipine or nitrates, was studied in a randomized trial. There was added benefit in treating anal fissure with a 0.4% topical nitroglycerin ointment for 80 days, compared with 40 days. Fissure healing and pain improvement continued until 6 weeks of treatment but were unlikely thereafter [15]. In this study, however, 30% of patients in the LNL group had pain improvement rating the pain as weakest (VAS score 1) at week 12 at the end of the study, twice as long as in aforementioned study.

In a quasi-experimental study carried out during one year and published in 2018, sixty consecutive cases with a clinical diagnosis of PCAF were recruited and randomly assigned to one of the two groups with first managed conservatively using topical 2% diltiazem ointment, yet the second group underwent open partial lateral internal sphincterotomy. Both groups were followed up for 6 weeks after the treatment. No pain was experienced by 17 (48.6%) patients after topical 2% diltiazem use [16]. The authors state that, although 2% diltiazem was less effective in healing the fissures, it was quite effective in reducing the symptoms and minimizing the pain when used. Once 2% diltiazem was discontinued, pain recurred only in a few patients. With regard to symptoms and minimizing the pain, our experience shows that LNL was less effective compared to ITBT (p=0.018).

Antropoli et al. [17] used topical nifedipine and reported that pain disappeared in 60% of the patients and decreased in an additional 30% after 21 days of treatment, contributing the high rate of total positive responders to nifedipine therapy (≈90%). The total number of responders in this study, regarding pain reduction, in the LNL group was comparable and even higher (100%), while there were no subjects with complete pain disappearance.

Different studies comparing two or three different types of treatment showed some degree of positive effect on pain by all investigated forms of therapy. Thus, in a randomized, double-blind trial including 90 patients with anal fissure divided in 3 groups, received local therapy of ointments containing 5% lignocaine (n=28), 0.5% minoxidil (n=36), or both (n=26). Even all three forms of therapy exhibit some degree of pain reduction, the minoxidil-lignocaine combination led to the best pain relief (82%) at week 6 at the end of the treatment [18]. In another double-blind clinical study, where patients were divided in two groups of 35 subjects, one treated with nifedipine and the other with isosorbide dinitrate, despite the differences in pain, a significant reduction was confirmed in both groups [19]. In a randomized controlled trial [20] a total of 38 patients were studied. Seventeen patients were randomized to receive ITBT, and the rest received a sphincterotomy. At 2 weeks postoperatively, the average score in the ITBT group was 2.5, while the score in the sphincterotomy group was 0.7 (p = 0.030). However, when comparing the average pain scores at day 1 versus 2 weeks in both groups, there was a significant decrease, thus demonstrating that both procedures resulted in symptomatic improvement. In the present study, during the analyzed period, from starting point to week 12, the pain intensity, measured as mild, medium and severe according to VAS, significantly decreased in all three groups, but the number of patients with only mild pain at the end of the study was highest (93.55%) in ITBT group.

The main limiting factor of our study was the 12 weeks follow-up period. This was not enough time to reflect upon any long-term results concerning pain treatment. In addition to the small sample size, another limitation is the use of a controlled retrospective prospective and longitudinal instead of randomized controlled study design.

CONCLUSION

Pain is a prognostic factor that directly affects the course of the disease. Its duration before treatment plays a significant role as a negative predictive factor of the treatment outcome.

The treatment failure was significantly influenced by the pain duration before the beginning of therapy. Namely, pain duration was longer in all patients referred for surgical treatment.

Injection therapy with botulinum toxin A is superior to anal dilation and local nifedipine in

combination with lidocaine in pain treatment of PCAF. However, further well designed and long enough randomized trials are needed for the valid estimation of the efficacy of injection therapy with botulinum toxin in this therapeutic indication among patients with PCAF.

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Резиме

ВРЕДНОСТ НА ИНЈЕКЦИСКАТА ТЕРАПИЈА СО BOTULINUM TOXIN ВО ТРЕТМАНОТ НА БОЛКАТА КАЈ ПРИМАРНИТЕ ХРОНИЧНИ АНАЛНИ ФИСУРИ ВО СПОРЕДБА СО АНАЛНА ДИЛАЦИЈА И ЛОКАЛЕН НИФЕДИПИН ВО КОМБИНАЦИЈА СО ЛИДОКАИН

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Вовед: Аналната фисура претставува надолжен расцеп на слузницата на аналниот канал што се протега од надворешниот анален отвор во насока на назабената линија на внатрешниот анален отвор. Фисурите се делат на примарни и секундарни, и на акутни или хронични. Покрај минималното ректално крвавење, чешање и неконтролирана анална секреција, примарните хронични анални фисури (ПХАФ) доминантно се манифестираат со анална болка, како нивна главна детерминанта. Болката се опишува како највознемирувачки симптом.

Цел: Да се спореди ефектот на инјекциската терапија со ботулинскиот токсин А (ИТБТ) наспроти аналната дилатација (АД) и локалниот нифедипин во комбинација со лидокаин (ЛНЛ) во третманор на болкара кај ПХАФ.

Материјал и методи: Оваа контролирана ретроспективно-проспективна лонгитудинална студија вклучува 94 пациенти поделени во 3 групи. Првата беше третирана со ИТБТ, втората со АД и третата со примена на ЛНЛ (31, 33 и 30 пациенти, соодветно). Во студијата беше употребен Clostridium botulinum токсин А, растворен со физиолошки раствор до концентрација од 200 U/ml. Растворот беше инјектиран на двете страни на ПХАФ во доза од 40 U. Аналната дилатација беше правена со видоизменета техника со примена на 3 прсти од едната рака, прогресивно внесувани во аналниот канал еден по друг, што беше проследено со постепена латерална дистракција во текот на 1 мин. Терапијата со ЛНЛ беше спроведена со примена на нифедипин (0,3 %) во форма на маст во комбинација со лидокаин (1,5 %), што беше аплицирано двапати дневно во текот на 3 недели. За мерење на болката беше користена визуелна аналогна скала (ВАС). Периодот на следење изнесуваше 12 недели со прв контролен преглед во 4-тата недела.

Резултати: Средната возраст на учесниците беше 46,6 ± 13,9 години (50 мажи наспроти 44 жени). Типот на терапијата имаше значително различен ефект врз болката во 4-тата недела ($p = 0,0003$). Тешка болка беше присутна само кај двајца пациенти со ИТБТ, 16 со АД и 6 пациенти со ЛНЛ. Пост хок анализата покажа различно време на исчезнување на болката до 12-тата недела ($p < 0,0001$). Просечното време беше најкратко во ИТБТ-групата (6,1±1,5 недели). Интензитетот на аналната болка значително се разликуваше во 3 групи (Fisher exact, $p = 0,002$). Имено, 71 % во ИТБТ-групата ја оценија болката како најслаба (ВАС-скор 1) во споредба со 18,2 % во АД и 30 % од пациентите во ЛНЛ-групата. Севкупната сигнификантност за намалување на болката во корист на ИТБТ се должеше на разликите меѓу ИТБТ- и АД-групата ($p = 0,00024$) и ИТБТ- во споредба со ЛНЛ-групата ($p = 0,018$).

Заклучок: Инјекциската терапија со ботулински токсин А е супериорна во однос на АД- и ЛНЛ-терапијата во намалувањето на болката кај пациенти со ПХАФ.

Клучни зборови: примарни хронични анални фисури, анална болка, инјекциска терапија со ботулински токсин А, анална дилатација, локален нифедипин во комбинација со лидокаин