World Journal of Surgery and Surgical Research

Research Article
Published: 25 Oct, 2023

Acute and Chronic Anal Fissure: The Role of a New Multitarget Ointment

Giani I[1], Cioppa T[2], Caminati F[1], Linari C[3], Dreoni P[4], Rossi G[4], Bettazzi F[5], Aprile A[5], Grassi S[5], Pede A[5] and Elbetti C[1]*

[1]SOSD Proctologia, Azienda USL Toscana Centro, Italy

[2]SOC Chirurgia Generale, Ospedale San Giuseppe-Empoli, Italy

[3]SOC Chirurgia, Ospedale Santa Maria Nuova-Firenze, Italy

[4]SOC Chirurgia Generale, Ospedale Santo Stefano-Prato, Italy

[5]Professional Nurses, USL Toscana Centro, Italy

Abstract

Introduction: Anal fissures are an extremely common disease with a severe impact on patients' quality of life. The main goal of anal fissure treatment is rapid pain relief and long-lasting healing. Recently, various local ointments have been proposed in the treatment of anal fissure. The aim of this study is to evaluate the efficacy of a new multitarget ointment consisting of 4 main active ingredients (Dermonectin, Argirelox, SymSitive and SynCalmin).

Methods: In this observational study the evaluated patients were divided into two groups: Acute and chronic fissures. Patients were instructed to apply the new multitarget ointment every 8 h for 1 month. The first endpoint was the rapid reduction of maximum anal pain intensity and the stabilization of the results in the follow-up. The secondary endpoints were the reduction in bleeding, mean pain intensity, maximum pain duration and relief of specific symptoms. Patient satisfaction was recorded. The number of patients healed was recorded, according to a published re-epithelization score.

Results: During the 9-month observational period, 103 of the 109 patients completed the treatment period. The maximum anal pain intensity at baseline was 7.99 while after 1 month, it was 3.33. Complete resolution of bleeding was achieved in 95% of cases after 1 week. The mean anal pain intensity at baseline (5.6) significantly reduced at 1 month (1.9). Significant reduction of maximum pain duration was recorded. The mean patient satisfaction rate was 8.2 (0-10). At 1 month no patients had deep fissures, 19 patients had a superficial fissure, 38 presented partial re-epithelization and 46 complete healing.

Discussion: In recent years, the focus has shifted to creams for local use, developed with the aim of interrupting the vicious circle underlying the pathophysiology of the fissure. Our study underlined the safety and efficacy of this multitarget ointment and its impact on different types of anal fissure. Its key components achieved all their objectives: Dermonectin promoted the healing process; Argirelox reduced anal hypertonus, promoting healing and reducing pain; SymSitive reduced pain and burning; and SynCalmin acted on the inflammatory process. The synergy of these four active ingredients was therefore a winner.

OPEN ACCESS

Correspondence:
Caminati Filippo, SOSD Proctologia, Azienda USL Toscana Centro, Prato, Italy

Received Date: *01 Oct 2023*
Accepted Date: *20 Oct 2023*
Published Date: *25 Oct 2023*

Citation:
Giani I, Cioppa T, Caminati F, Linari C, Dreoni P, Rossi G, et al. Acute and Chronic Anal Fissure: The Role of a New Multitarget Ointment. World J Surg Surgical Res. 2023; 6: 1506.

Introduction

Anal fissures have a severe impact on patients' quality of life [1]. The main symptom is anal pain, which can be acute or chronic, recurrent and extremely disabling. The most common sign is anal bleeding, due to delayed healing of the fissure or local trauma, mostly occurring during bowel movements.

The main goal of anal fissure treatment is rapid pain relief and long-lasting healing of the fissure. It also aims to avoid evolution towards an abscess or perianal fistula, through effective healing and appropriate timing of the treatment, as well as to reduce indications for surgery, notwithstanding the recent introduction of less invasive procedures [2].

Anal fissures are extremely common worldwide and are estimated to account for 10% to 15% of all proctologic consultations [3]. The incidence in the United States is approximately 342,000

cases, mostly in young or middle-aged patients [4]. They often occur after a local trauma, such as passing hard stools or a bout of diarrhea [5,6]. The internal anal sphincter reacts by increasing its tone and, consequently, resting anal pressure; this is followed by a reduction in local blood supply and ultimately to an inability to heal quickly and effectively [7-9].

Anal fissures can be divided into two main categories, depending on the duration of symptoms: Acute anal fissure, where symptoms arose in the last 6 weeks, and chronic anal fissure, for symptoms of a longer duration. Within the group of chronic fissures, however, the objective features of the wound must also be carefully evaluated, as it may sometimes be complicated by the presence of sentinel skin tags, anal papillae, anal polyps and indurated margins [10,11].

In recent decades, various local ointments have been proposed to reduce anal pressure and/or to control anal pain, as well as to enable the fissure to heal through the application of active substances [12] and improvement of the blood supply. The aim of this study is to evaluate the efficacy of a new multitarget ointment consisting of 4 main active ingredients (Dermonectin, Argirelox, SymSitive and SynCalmin), each with a specific goal, on anal fissure in terms of pain control, symptoms resolution, healing time and patient satisfaction.

Materials and Methods

This is an observational study including all consecutive patients affected by acute or chronic anal fissure evaluated from January 2022 to September 2022. Patients enrolled from 5 different hospitals affiliated with USL Toscana Centro (Presidio Palagi-Firenze, Ospedale San Giuseppe-Empoli, Santa Maria Annunziata-Bagno a Ripoli, Ospedale Santa Maria Nuova-Firenze, and Ospedale Santo Stefano-Prato) were included in the study. All participants provided their verbal and written informed consent to participation in the study. They underwent a complete medical history, clinical evaluation, proctologic physical examination, Anoscopy and endo-anal ultrasound at their initial outpatient clinical examination (T0) and at 1 week (T1), 2 weeks (T2) and 1 month (T3) thereafter, as presented in Table 1.

Patients were evaluated together (group AA) and then divided into two main groups according to the duration of symptoms: Acute anal fissure (group A), comprising patients with symptoms arising within the previous 6 weeks, and Chronic anal fissure (group C), with symptoms arising earlier than 6 weeks previously [10,11]. Group C was then further subdivided by clinical presentation into patients with chronic anal fissures complicated by the presence of fibrotic sentinel piles or skin tags (group CC), and patients with simple chronic fissure (group SC).

The study was conducted in accordance with the protocol, the ethical principles deriving from the Declaration of Helsinki, applicable ICH standards of Good Clinical Practice, and applicable laws and regulations.

Aims and scope

The first endpoint was a progressive evaluation to demonstrate the rapid reduction (1 week) of maximum anal pain intensity (Maximum VAS) and the stabilization of the results in the subsequent follow-up (2 weeks and 1 month) [13]. The secondary endpoints were the reduction in bleeding (Giamundo score [14]), mean pain intensity (VAS 0-10) and maximum pain duration (1 - less than 10 min, 2- between 10 and 30 min, 3- between 30 and 60 min, 4- more than 60 min) and relief of specific symptoms, measured with the REALISE score [15] at 1, 2 and 4 weeks. The number of patients complaining of specific symptoms, such as pain, bleeding, itching and burning, was also recorded.

Patient satisfaction at 1 month was recorded through a simple satisfaction score (0-10) and treatment efficacy was evaluated in relation to analgesic use, any changes in treatment strategy or transition to surgery. The number of patients healed at T3 was recorded, with patients graded according to a previously published re-epithelization score (0- deep fissure still present, 1- superficial fissure, 2- partial re-epithelization, 3- complete healing and re-epithelization) [16]. Digital anal exploration by the surgeon was graded on a specific scale as 0 ("no pain"), 1 ("exploration painful") or 2 ("exploration impossible"). Ointment safety was evaluated through logging of any short-term complications and allergic reactions.

Treatment protocol

Patients were instructed to apply the new multitarget ointment circumferentially up to 1 cm to 2 cm inside the anus with the tip of a finger every 8 h for the entire 1-month study period. Warm sitz baths and use of oral analgesics as needed were suggested in the event of acute pain [17,18]. Patients were advised to follow a high-fiber diet, drink plenty of water and avoid anal sex during the observation period.

Inclusion and exclusion criteria

Adult patients reporting anal pain secondary to a single anal fissure who were able to understand all medical instructions and adhere to our protocol were included. The exclusion criteria were as follows: Previous proctologic surgery or radiotherapy, concomitant colorectal disease (hemorrhoids, perianal abscess or anal fistula, condyloma acuminata, Crohn's disease, ulcerative rectocolitis, chronic diarrhea, constipation requiring manual manoeuvres during evacuation, anal neoplasms, fecal incontinence, proctitis), HIV infection, severe systemic diseases, uncontrolled comorbidities such as diabetes or kidney failure, anticoagulant therapy, pregnancy and age under 18 years.

Patients were withdrawn from the study in the event of failure to follow the protocol, failure to apply the ointment, hypersensitivity to the product, change in treatment strategy, further surgery during or at the end of the follow-up period, or at their own request. They were offered different conservative treatments or surgery, when indicated.

Statistical analysis

The statistical analyses focused on post-treatment results of the multitarget ointment treatment in a selected patient group: The clinical and follow-up data were stored in a prospective maintained database. Categorical variables were analyzed and reported as counts and percentages, and as the mean ± SD (range) for continuous normally distributed variables, whereas ordinal categorical variables and continuous non-normally distributed variables were reported as median [Confidence Interval]. The chi-square test was used for cross tabulations. Results with $p < 0.05$ were considered statistically significant. XLSTAT software (version 2021.3.1) (Addinsoft PARIS, France) was used for the statistical analysis.

Results

During the 9-month observational period, 103 of the 109 patients (60 women, mean age 48.3 years, range 21-78) completed the treatment period and were evaluated. Six patients dropped out from

Table 1: Data collection.

	T0	T1	T2	T3
	Preoperative	1 week	2 weeks	1 month
Acute anal fissure (yes-no)	√	-	-	-
Chronic anal fissure (yes-no)	√	-	-	-
Chronic complicated anal fissure (with fibrotic sentinel pile or skin tag) (yes-no)	√	-	-	-
Anal Fissure Position (12 o'clock position for anterior and 6 for posterior)	√	-	-	-
Pain (yes-no)	√	√	√	√
Bleeding (yes-no)	√	√	√	√
Anal itching (yes-no)	√	√	√	√
Burning (yes-no)	√	√	√	√
Constipation (yes-no)	√	√	√	√
Diarrhea (yes-no)	√	√	√	√
Anal intercourse (yes-no)	√	√	√	√
Duration of symptoms (months)	√	-	-	-
BLEEDING Score (Giamundo)	√	√	√	√
REALISE Score	√	-	√	√
Mean Pain (VAS 0-10)	√	√	√	√
Maximum Pain (VAS 0-10)	√	√	√	√
Maximum Pain Duration				
1-Within 10 minutes				
2-Between 10 and 30 minutes	√	√	√	√
3-Between 30 and 60 minutes				
4-More than 60 minutes				
Anal Digital Exploration				
0-not painful				
1-painful	√	-	√	√
2-impossible				
Degree of re-epithelization				
0-deep fissure still present				
1-superficial fissure	√	-	√	√
2-partial re-epithelization				
3-complete healing and re-epithelization.				
Adverse events (yes-no)	-	√	√	√
Pain or Burning at Ointment application	-	√	√	√
Allergic Reaction	-	√	√	√
Pain killer consumption	√	√	√	√
Treatment Strategy Change	-	√	√	√
Surgery (yes-no)	-	√	√	√
Patient Satisfaction (VAS 0-10)	-	√	√	√

the study as they were unable to apply the ointment. Thirty patients had acute fissures and 73 had chronic fissures, associated in 35 cases with fibrotic sentinel piles or skin tags.

First endpoint

Maximum anal pain intensity (Table 2): Considering all patients, the maximum anal pain intensity at baseline (AA Max Pain T0) was 7.99 while after 1 month (T3) it was 3.33 ($p<0.001$), with an overall success rate of 92% (95/103). Reduced pain was also observed at T1 and T2, and was more evident in group A (Figure 1).

Secondary endpoints

Giamundo bleeding score (Table 3): There was already a highly statistically significant reduction in bleeding at T1 ($p<0.001$), remaining stable thereafter: Complete resolution of bleeding was in fact achieved in 95% of cases (98/103) after 1 week. The Giamundo score remained stable at T2 and T3. In group CC only, recurrence of bleeding was observed after 4 weeks, probably due to the difficulty in achieving stable healing of chronic fissures; however, this was not statistically significant.

Table 2: Maximum and Mean anal pain intensity (VAS 0-10), Realise Score. AA: All, A: Acute, AAC: All Chronic, CS: Chronic Simple, CC: Chronic Complicated.

	Maximum Pain - (VAS 0-10)					Mean Pain - (VAS 0-10)					Realise Score				
	AA	A	AAC	CS	CC	All	A	AC	SC	CC	All	A	AC	SC	CC
T0 Pre treatment	7.9	7.9	7.8	7.8	7.8	5.6	5.8	5.6	5.8	5.4	15.7	15.7	14.4	13.8	15
T1 1 week	5.4	5.8	5.3	5.7	5	3.5	3.3	3.7	4	3.4	9.8	9.4	9.9	9.5	10.4
T2 2 weeks	4.4	3.4	4.9	5.2	4.9	2.8	1.8	3.2	3	3.4	8.2	6.9	8.8	8.1	9.8
T3 1 month	3.3	2.8	4.4	4.8	4.6	1.9	1.1	2.7	1.8	3.2	6.9	6.4	7.1	5.3	9
p	P<0.001					P<0.0001					P<0.001				

Table 3: Giamundo Bleeding Score. AA: All, A: Acute, AAC: All Chronic, CS: Chronic Simple, CC: Chronic Complicated.

Giamundo Score	T0 – Pre Treatment					T1 – 1 week					T2 – 2 weeks					T3 – 1 month				
	AA	A	AAC	CS	CC	AA	A	AAC	CS	CC	AA	A	AAC	CS	CC	AA	A	AAC	CS	CC
0	32	3	29	22	7	80	18	62	34	28	92	23	69	33	36	81	27	54	34	20
1	0	0	0	0	0	11	3	8	0	8	8	3	5	5	0	10	3	7	0	7
2	20	3	17	11	6	9	9	0	0	0	3	3	0	0	0	5	0	5	5	0
3	35	21	14	0	14	0	0	0	0	0	0	0	0	0	0	7	0	7	0	7
4	15	3	12	5	7	5	0	5	5	0	5	0	5	5	0	0	0	0	0	0

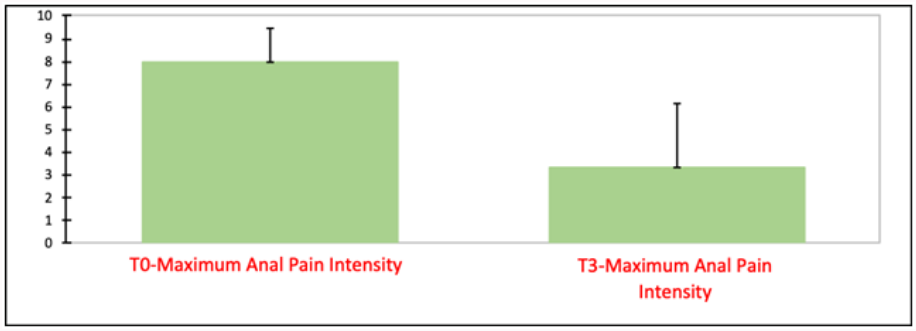

Figure 1: Maximum anal pain intensity (all patients) at T0 and T3.

Table 4: Symptoms (number of patients) changes between the Groups. AA: All, A: Acute, AC: All Chronic, SC: Simple Chronic, CC: Complicate Chronic.

	Pain					Anal Itching					Burning					Bleeding				
	AA	A	AC	SC	CC	AA	A	AC	SC	CC	AA	A	AC	SC	CC	AA	A	AC	SC	CC
T0 Pre treatment	103	30	73	38	35	12	0	12	5	7	57	15	43	22	21	71	27	44	16	28
T1 1 week	72	24	48	24	24	5	0	5	5	0	56	12	44	22	22	34	15	19	5	14
T2 2 weeks	63	21	42	21	21	12	0	12	5	7	42	6	36	22	14	18	6	12	5	7
T3 1 month	52	15	37	16	21	0	0	0	0	0	21	3	18	11	7	15	3	12	5	7
p	P <0.007					P=0.089					P<0.008					P<0.01				

Mean pain intensity (Table 2)

Considering all patients, the mean anal pain intensity at baseline (T0) was 5.6 and at T3 was 1.9 (p<0.001). This reduction was less evident in group CC and more pronounced in group SC.

Maximum pain duration

Pain duration was categorized as follows: 1- less than 10 min, 2- between 10 and 30 min, 3- between 30 and 60 min, 4- more than 60 min. The maximum pain duration at T0 was more than 60 min in 20 patients, between 30 and 60 min in 3 patients, between 10 and 30 min in 30 patients and less than 10 min in 50 patients. At T3 all patients reported a significant reduction to category 1, less than 10 min. Significant reduction of maximum pain duration.

REALISE score (Table 2)

At baseline (T0), the mean REALISE score for all patients was 15.7, with 41 patients (26 with chronic fissure and 15 with acute fissure) scoring above the mean. At T1, 93 patients were under the T0 mean value and at T2 and T3, all patients had reached a standard normalization under the T0 mean value (Group AA REALISE score at T3=6.9). This difference was highly statistically significant (p<0.001). When broken down by subgroup, the reduction was found to be greatest in Group A, and less pronounced in Group CC (Figure 2).

Symptoms: Pain, anal itching, burning, bleeding (number of patients) (Table 4)

Considering all patients, there was a significant reduction in anal pain between T0 and T3 (p<0.007). This reduction was less evident in group CC, probably due to the reduced treatment efficacy in complicated chronic fissures. Anal itching was reported at T0 by just 12 of the initial 103 patients (11.6%) and had completely disappeared by T3. Burning was reported by 57 patients (55.3%) at T0. This

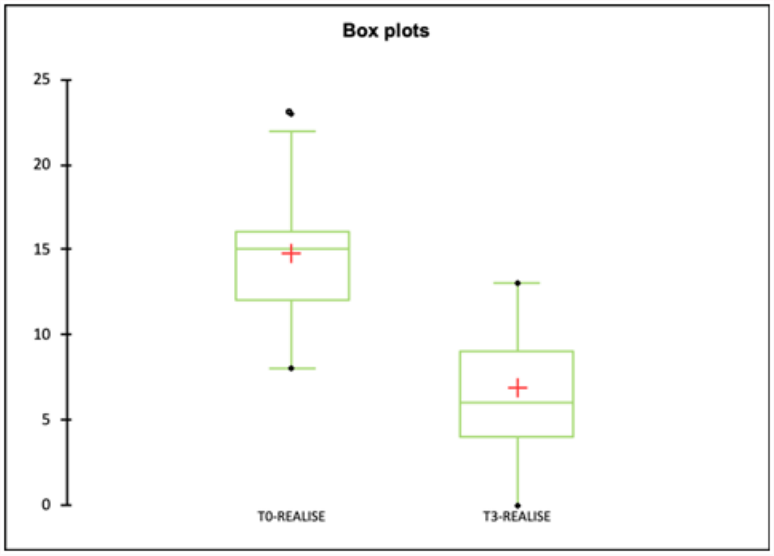

Figure 2: REALISE score (all patients) at T0 and T3.

Table 5: Degree of re-epithelization (number of patients). AA: All, A: Acute, AAC: All Chronic, CS: Chronic Simple, CC: Chronic Complicated.

Degree	0-deep fissure still present					1-superficial fissure					2-partial re-epithelization					3-complete healing and re-epithelization.				
	AA	A	AAC	CS	CC	AA	A	AAC	CS	CC	AA	A	AAC	CS	CC	AA	A	AAC	CS	CC
T0 Pre treatment	40	9	31	10	21	50	21	29	22	7	13	0	13	6	7	0	0	0	0	0
T3 1 month	0	0	0	0	0	19	0	19	5	14	38	15	23	16	7	46	15	31	17	14

Table 6: Most important statistical results.

	T0 – Pre Treatment	T1 – 1 week	T2 – 2 weeks	T3 – 1 month	p
Bleeding (number of Patients)	71	23	11	22	<0.001
Mean Pain (VAS score 0-10)	5.86	3.6	2.81	1.96	<0.0001
Maximum Pain (VAS score 0-10)	7.99	5.49	4.48	3.33	<0.001
Maximum Pain duration (minutes)	180	89	76	88	<0.001
Realise score	15.7	9.8	8.2	6.9	<0.001

dropped to 21 patients at T3 ($p<0.008$), a success rate of 63.2%, rising in group A to 80%. Bleeding was observed in 71 patients (68.9%) at T0, dropping to 15 patients at T3, a reduction of 78.9% ($p<0.01$). The best result was obtained in group A, with a success rate of 88.9%.

Satisfaction - analgesic use - changes in treatment strategy - transition to surgery

At T3, the mean satisfaction rate was 8.2 (range 0-10). Satisfaction was lowest (7.4) in group CC. No patients reported use of analgesics at T3. An unsatisfactory result, leading to an indication for surgery or further treatment, was observed in no patients in group A, 13/35 (37%) in group CC and 10/38 (26%) in group SC.

Anal fissure healing (Table 5)

At T0, 40 patients had a deep fissure, 50 a superficial fissure and 13 (in Group C) partial re-epithelization. At T3 no patients had a deep fissure, 19 patients (14 in the CC group and 5 in the SC group) had a superficial fissure, 38 presented partial re-epithelization and 46 presented complete healing.

Considering Group A, 9 at T0 9 patients presented with deep fissure and 21 with superficial fissure (21 patients), while at T3 all had improved to partial re-epithelization (15 patients) or complete healing and re-epithelization (15 patients).

Digital anal exploration

At T0, due to pain, digital anal exploration was performed only after local anesthetic injection in 68 patients (66%), 47 in Group A and 21 in Group C.

By T3, digital exploration was still impossible in just 18 patients (17%). This result demonstrates the successful reduction in pain and was statistically significant ($p<0.01$) on the Chi-square test.

Safety of the new multitarget ointment

Any local or systemic allergic reactions were recorded. One patient reported itching after 2 weeks of application, but continued the treatment anyway.

Dropouts

Six patients (3 women) with an average age of 31.3 (range 19-55) left the study: 4, suffering from acute fissure, were unable to apply the cream due to pain; and 2, with complicated chronic fissures, specifically asked to undergo surgery during the treatment period. The dropout rate was thus 5.5% for patients as a whole, 13.3% for Group A and 5.7% for Group CC.

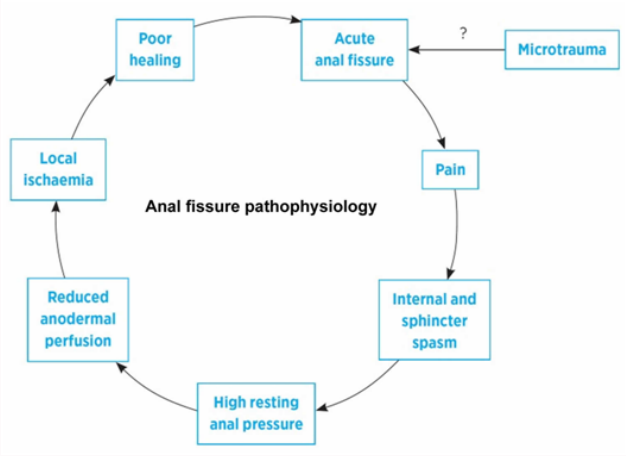

Figure 3: Anal fissure pathophysiology [7].

All the most important and statistically significant results are reported in Table 6.

Discussion

The medical history of patients with anal fissures can be very varied. Some patients report a single previous episode that they had ignored at the time and only remembered when specifically questioned, some experience such intense acute pain that they quickly decide to consult a specialist, and others report recurring episodes of anal pain over months or even years before they finally decide to undergo a proctological examination.

The pathophysiology of anal fissure has been studied extensively and the diagram proposed by Madalinski [7] is very clear and straightforward (Figure 3). Various key moments in the pathophysiological pathway thus emerge that can be the target of treatment.

In the literature, the use of warm sitz baths is commonly advised to reduce idiopathic or reactive hypertension of the internal anal sphincter [19], and a high-fiber diet and drinking plenty of water [20] is also advised, to loosen the stools and hence reduce the mechanical trauma of defecation caused by hard stools. Finally, the use of local creams to protect the anal canal (including against diarrhea) and promote healing is recommended. In the event of failure or only partial success of these strategies, surgery becomes the only solution: Sphincterotomy (to date still the gold standard) has even better results than medical therapy, but carries a risk of fecal incontinence [21].

In recent years, the focus has shifted to creams for local use, designed and developed with the aim of interrupting the vicious circle underlying the pathophysiology of the fissure. Different pharmacologic agents, such as topical nitrates or calcium channel blockers, have been suggested to reduce anal pressure and increase blood flow, with slightly better results than placebo on healing rate outcome, but with unpleasant side effects such as headache or migraine as well as pruritus ani [22-24].

The effectiveness of botulinum toxin injection has also been evaluated. It produced good results but also showed limitations in terms of adequate dosage, precise site and number of injections [12-25].

On the basis of the results in the literature and the pathophysiological pathway underlying anal fissure, a new ointment was developed to act on several aspects contemporaneously in order to interrupt the pathophysiologic vicious circle. This multitarget ointment aims to promote the healing process, reduce anal tone by stimulating myorelaxation of the internal anal sphincter, control anal pain and modulate the inflammatory process. Its key active ingredients are as follows:

Dermonectin, a new-generation peptide that increases mucosal skin elasticity by stimulating the synthesis of fibronectin, a protein naturally present in the dermis, while performing a repairing action [26].

Argirelox™, a complex of low molecular weight oligopeptides (acetyl hexapeptide-8 and pentapeptide-18) with 'Botox-like' activity, which modulates muscle contractions by reducing Acetylcholine (ACh) release from the fusion of the fixed vesicles to the cellular membrane in the SNARE complex [27-29]. These peptides are already an effective adjuvant to Botox cosmetic injections in anti-wrinkle treatment [30];

SymSitive [31], which acts directly on the nociceptive system by alleviating anal hyperalgesia, working on symptoms such as stinging pain and burning.

SynCalmin [32], a synthetic oat derivative with antihistamine, anti-inflammatory, anti-itching and antioxidant activity.

Our study demonstrated the efficacy on anal fissures of this new multitarget ointment, which provided excellent pain control, achieving a 92% success rate on maximum anal pain intensity, particularly in patients with acute anal fissure (group A). Its efficacy in reducing pain was also confirmed by the drop in mean pain intensity and maximum pain duration, as well as by the ability to carry out digital anal exploration at the end of the treatment period. Bleeding, present in 68.9% of the patients at the baseline, was also reduced drastically as early as 1 week after the start of treatment.

The REALISE score, a recently introduced measurement tool based on the analysis of several clinical parameters, showed a statistically significant reduction in various symptoms above all in Group A, and less so in group CC. The effect on the healing process was measured by clinical examination 30 days after the start of therapy: 46 patients showed complete healing, and no patient had a persistent deep fissure. Healing was particularly evident in Group A. Finally, patient satisfaction was explored by means of a simple Visual Analogue Scale,

which recorded a mean value of 8.2, as well as through the need for surgery or further treatment. This last parameter was fundamental, as it showed that patients with acute anal fissures were able to stop the treatment after 30 days, while 13 of the 35 patients with complicated chronic fissures and 10 of the 38 patients with simple chronic fissures required further treatment, or even surgery.

A number of considerations must be made in relation to the various patient groups. Four of the 30 patients with acute anal fissure were unable to take part in the study, due to intense pain resulting in an inability to apply the cream. This finding must be taken into account, and highlights the importance of adherence to therapy for achieving the desired results. There is a clear need to find a different strategy for such patients, which, however, amounted to just 11.7% of our sample. This notwithstanding, the best results were generally observed in patients with acute fissures.

In contrast, the success rate, while still good, was lower in patients with complicated chronic fissures, probably due to the local presence of fibrous and inelastic tissue, which is less responsive to the treatment. In fact, this group required further treatment, including surgery, which now offers excellent healing with or without internal sphincterotomy, thanks to the use of new techniques such as the CO_2 laser scanner [2].

Limitations of the Study

This multicenter study reports, for the first time, the results of a new multitarget ointment in the treatment of anal fissure. Its main limitations are that it was not a randomized prospective study and it involved only a short observation period. However, its excellent outcomes offer a promising basis for the development of future comparative studies. These results need to be confirmed through multicenter randomized trials conducted for a longer period, to highlight the role, timing and effectiveness of conservative therapies in the treatment of anal fissure.

Conclusion

The development of new products aiming to correct several key points of the pathophysiology of anal fissure has made it possible to transversely treat any type of patient suffering from anal fissure. Our study underlined not only the safety and efficacy of this multitarget ointment but also its impact on different types of anal fissure. Its key components achieved all their objectives: Dermonectin promoted the healing process; Argirelox reduced anal hypertonus, promoting healing and reducing pain; SymSitive reduced pain and burning; and SynCalmin acted on the inflammatory process. The synergy of these four active ingredients was therefore a winner.

References

1. Sailer M, Bussen D, Debus ES, Fuchs KH, Thiede A. Quality of life in patients with benign anorectal disorders. Br J Surg. 1998;85:1716-9.
2. Giani I, Cioppa T, Linari C, Caminati F, Dreoni P, Rossi G, et al. Scanner-assisted CO_2 laser fissurectomy: A pilot study. Front Surg. 2021;8:799607.
3. Newman M, Collie M. Anal fissure: Diagnosis, management, and referral in primary care. Br J Gen Pract. 2019;69(685):409-10.
4. Mapel DW, Schum M, Von Worley A. The epidemiology and treatment of anal fissures in a population-based cohort. BMC Gastroenterol. 2014;14:129.
5. Beaty JS, Shashidharan M. Anal Fissure. Clin Colon Rectal Surg. 2016;29(1):30-37.
6. Gardner IH, Siddharthan RV, Tsikitis VL. Benign anorectal disease: Hemorrhoids, fissures, and fistulas. Ann Gastroenterol. 2020;33(1):9-18.
7. Madalinski MH. Identifying the best therapy for chronic anal fissure. World J Gastrointest Pharmacol Ther. 2011;2(2):9-16.
8. Schouten WR, Briel JW, Auwerda JJ. Relationship between anal pressure and anodermal blood flow. The vascular pathogenesis of anal fissures. Dis Colon Rectum. 1994;37(7):664-9.
9. Schouten WR, Briel JW, Auwerda JJ, De Graaf EJ. Ischaemic nature of anal fissure. Br J Surg. 1996;83(1):63-5.
10. Chong PS, Bartolo DC. Hemorrhoids and fissure in ano. Gastroenterol Clin North Am. 2008;37:627-44.
11. Lindsey I, Jones OM, Cunningham C, Mortensen NJ. Chronic anal fissure. Br J Surg. 2004;91:270-79.
12. Jonas M, Scholefield JH. Anal fissure. Gastroenterol Clin North Am. 2001;30:167-81.
13. Hjermstad MJ, Fayers PM, Haugen DF, Caraceni A, Hanks GW, Loge JH, et al.; European Palliative Care Research Collaborative (EPCRC). Studies comparing numerical rating scales, verbal rating scales, and visual analogue scales for assessment of pain intensity in adults: a systematic literature review. J Pain Symptom Manage. 2011;41:1073-93.
14. Giamundo P, Braini A, Calabro' G, Crea N, De Nardi P, Fabiano F, et al. Doppler-guided Hemorrhoidal dearterialization with Laser (HeLP): A prospective analysis of data from a multicenter trial. Tech Coloproctol. 2018;22(8):635-43.
15. Picciariello A, Lobascio P, Spazzafumo L, Rinaldi M, Dibra R, Trigiante G, et al. The REALISE score: A new statistically validated scoring system to assess the severity of anal fissures. Tech Coloproctol. 202;25:935-40.
16. Martellucci J, Rossi G, Corsale I, Carrieri P, D'Elia M, Giani I. Myoxinol ointment for the treatment of acute fissure. Updates Surg. 2017;69:499-503.
17. Das SA. Concise Textbook of Surgery. 7th ed. Das Publications: Kolkata: 2012;1083-5.
18. Brunicardi FC. Schwartz's Principles of Surgery. 9th Ed. Singapore: The McGraw-Hill: 2011. p. 302.
19. Jiang JK, Chiu JH, Lin JK. Local thermal stimulation relaxes hypertonic anal sphincter: Evidence of somatoanal reflex. Dis Colon Rectum. 1999;42:1152-9.
20. Hananel N, Gordon PH. Re-examination of clinical manifestations and response to therapy of fissure-in-ano. Dis Colon Rectum. 1997;40:229-33.
21. Nelson RL, Thomas K, Morgan J, Jones A. Non surgical therapy for anal fissure. Cochrane Database Syst Rev. 2012;2:CD003431.
22. Jin JZ, Bhat S, Park B, Hardy MO, Unasa H, Mauiliu-Wallis M, et al. A systematic review and network meta-analysis comparing treatments for anal fissure. Surgery. 2022;172(1):41-52.
23. Latif A, Ansar A, Butt MQ. Morbidity associated with treatment of chronic anal fissure. Pak J Med Sci. 2013;29:1230-35.
24. Stewart DB Sr, Gaertner W, Glasgow S, Migaly J, Feingold D, Steele SR. Clinical practice guideline for the management of anal fissures. Dis Colon Rectum. 2017;60(1):7-14.
25. Lee TH, Marcantonio ER, Mangione CM, Thomas EJ, Polanczyk CA, Cook EF, et al. Derivation and prospective validation of a simple index for prediction of cardiac risk of major noncardiac surgery. Circulation. 1999;100:1043-9.
26. Singh P, Carraher C, Schwarzbauer JE. Assembly of fibronectin extracellular matrix. Ann Rev Cell Dev Biol. 2010;26:397-419.
27. Blanes-Mira C, Merino JM, Valera E, Fernández-Ballester G, Gutiérrez LM, Viniegra S, et al. Small peptides patterned after the N-terminus

domain of SNAP25 inhibit SNARE complex assembly and regulated exocytosis. J Neurochem. 2004;88(1):124-35.

28. Chen YA, Scheller RH. SNARE-mediated membrane fusion. Nat Rev Mol Cell Biol. 2001;2(2):98-106.

29. Gaj F, Bianchi FP, Passannanti D, Telesco D. Relief of hemorrhoid symptoms: Pilot study of a new topical ally. G Chir. 2020;41(1):118-25.

30. Benedetto AV. The environmental and skin aging. Clin Derm. 1998;16:129-39.

31. Schoelermann AM, Weber TM, Arrowitz C, Rizer RL, Qian K, Babcock M. Skin compatibility and efficacy of a cosmetic skin care regimen with licochalcone A and 4-t-butylcyclohexanol in patients with rosacea subtype I. J Eur Acad Dermatol Venereol. 2016;30(Suppl 1):21-7.

32. Blanchard G, Walker A, Dendooven E, Aerts O, Goossens A, Gilliet M, et al. Allergic contact dermatitis from a skin-calming cream containing hydroxyphenyl propamidobenzoic acid. Contact Dermatitis. 2023;88(1):68-70.