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Research Article

The Role of Fitostimoline Proctogel in Symptoms Relief and Healing in Patients Affected by Anal Fissure

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Abstract

Objective: evaluation of a new medical device product based on Rigenase®: Fitostimoline® Proctogel which could reduce the pain and favor tissue re-epithelialization by forming a protective barrier towards the anal area.

Methods: evaluation of 96 patients equally divided in 3 treatment groups: Group 1: Fitostimoline® proctogel 2 applications per day; Group 2: Fitostimoline® proctogel 2 applications per day, in addition to any other topical therapy chosen between the following: Levorag®, Antrolin® or Rectogesic®; Group 3: a product for topical use, at surgeon choice, between the following: Levorag®, Antrolin® or Rectogesic®.

At least one re-evaluation was performed within 1 month, at least a second re-evaluation within 2 months, final evaluation at 4 months. At each checkup, the surgeon filled out the data recording sheet (DRS)-A and the DRS-B, containing personal and clinical data (anamnestic and objectives) and DRS-C, D and E (if the consultation was not clinical, only the part relating to symptoms was filled out). A pharmacoeconomic analysis was also performed.

Results: During the second and third visit, a significant improvement of symptoms was observed in the groups 1 and 2 in respect to group 3. Both pain and bleeding were improved during the treatment course. Patients were highly satisfied by the treatment with Fitostimoline® Proctogel in respect to the other treatments both in terms of efficacy and in cost.

Conclusions: Fitostimoline® proctogel could be a new efficacious and economic tool which can be used for the treatment of fissures.

Introduction

Anal fissure is one of the most common anorectal conditions causing intense anal pain; it's often misdiagnosed as hemorrhoidal disease and it is associated to reduced quality of life and loss of working hours. Anal fissure is a longitudinal tear at the epithelial lining of the anus. The primary method for diagnosing anal fissures is by physical examination with the finding of a teared lesion (tipically posterior at the commissura posterior), often accompanied by a sentinel skin tag and sphincter hypertonicity. During defecation, stretching of the lesion causes severe pain, that can last hours after defecation; bleeding is also often present . Some 50% of patients experience additional symptoms such as swelling, prolapse, pruritus, and mucosal discharge. This condition occurs in all age groups, and it is equally prevalent in men and women. Anal fissures with symptoms that persist longer are classified as chronic anal fissure. The possible mechanism for acute anal fissure is straining during defecation, leading to trauma and sphincter hypertonicity which makes the healing process difficult. At that point, a vicious circle is established characterized by pain and anal sphincter hypertonicity, that maintains the fissure open.

The majority of anal fissures are acute and resolve spontaneously [10] or within 6-8 weeks of medical treatment [11]. Acute anal fissure is often treated through the ingestion of bulking agents such as fibers, sitz baths and application of local ointments. [12] The available therapies are based on various topical therapies, aimed both at improving trophism, controlling pain, and reducing sphincter hypertonicity. The addition of topical ointments accelerates the healing process and prevents the progression to chronic anal fissure [13]. These topical drugs tipically include nitrates and calcium channel blockers (CCBs) that heal the fissure through relaxation of the anal sphincter [14,15] ; diltiazem and nifedipine with or without local anesthetic are typically prescribed in anal fissure. The addition of re-epithelializing agents alone or in combination with drugs that reduce sphincter hypertonicity is often used in the treatment of acute anal fissure; these products are natural and highly tolerated and could be used also in pregnancy with no counter indications. For these reasons, these natural devices could represent a new fronter in the treatment of anal fissures. In this trial, we evaluated a natural medical device product based on Rigenase® and Mucosave: Fitostimoline® Proctogel. Fitostimoline® devices are highly known for their re-epithelizing activity and are highly tolerated. In fact, Rigenase® is a particular triticum vulgare extract that gives to the product hydrating properties. Mucosave is a natural extract of olive leaves and prickly pear. The combination of these ingredients gives to the product its regenerating and anti-inflammatory activities. Fitostimoline® proctogel could reduce the pain and favour tissue re-epithelialization by forming a protective barrier towards the anal area.

Patients and Methods

Trial Design

The present study was approved by the ethical committee of ASST Cremona and the protocol is published on www.clinicaltrials.gov (ClinicalTrials.gov Identifier: NCT04714684).

Inclusion criteria were the presence of a symptomatic anal fissure in absence of previous therapies for anal fissure in subjects more than 18 years old, able to give informed consent; exclusion criteria were unability to give informed consent, the presence of anal fissure associated with other conditions (fistula-in-ano, inflammatory bowel disease, perianal sepsis or malignancy), a previous lateral sphincterotomy or anal stretch under general anesthesia, and ongoing pregnancy.

Patients were divided in 3 groups:

- Group 1: Fitostimoline® proctogel 2 applications per day, external, without applicator
- Group 2: Fitostimoline® proctogel 2 applications per day, external, without applicator, in addition to any other topical therapy chosen between the following: Levorag®, Antrolin® or Rectogesic®
- Group 3: a product for topical use, at surgeon choice, between the following: Levorag®, Antrolin® or Rectogesic®

All participating surgeons received a sealed envelope containing an equal number of fishes for group 1, 2 and 3. At the time of the visit, once the patient's consent has been obtained to participate in the study, the surgeon filled out the data recording sheet (DRS)-A and the DRS-B, containing personal and clinical data (anamnestic and objectives) respectively. Then the randomization was made, by extracting a fish from the randomization envelope. The administration of stool softeners and analgesic therapy (local or systemic) was allowed, at the complete discretion of the physician. The surgeon made an appointment for a check-up freely, but within these limits: at least one re-evaluation within 1 month, at least a second re-evaluation within 2 months, final evaluation at 4 months. The revaluations could also be performed by telephone, text message or email. At each checkup, the surgeon filled out the DRS-C, D and E (if the consultation was not clinical, only the part relating to symptoms was filled out).

Primary endpoints were:

1-Percentage of patients with improvement of symptoms at each check-up

2-Degree of improvement (pain expressed in NRS numerical scale, number of weekly bleeds)

3-Degree of overall patient satisfaction with the therapy (cost and effectiveness), expressed in the DRS-C, D and E. These data were collected through an interview made by physicians directly to patients in which they considered as satisfactory both the treatment efficacy and its cost on a scale from 0 to 10, in which 0 is absence of satisfaction and 10 is maximum satisfaction.

Secondary end points were:

1. Percentage of patients who required invasive therapies

2. Pharmaco-economic evaluation

Statistics and Sample Size

This is a non-inferiority study. Since Fitostimoline® proctogel is a low-cost product and substantially has no side effects, the purpose of the study is to demonstrate that Fitostimoline® proctogel is not inferior to other products in terms of studied end -points. Considering the results of a pilot study, it has been hypothesized that 70% of patients will reach the primary endpoint in all groups; based on this assumption, 32 patients will be needed in each group to be able to highlight a non-inferiority of 10% or more with an α error of 5% and a statistical power of 80%. The characteristics of the sample will be expressed in terms of absolute and relative frequencies (percentages) for what concerns the categorical variables, and through mean and standard deviation, or alternatively median and range if the distribution is not normal, for continuous quantitative variables. The comparison of the characteristics of the sample between the three groups will take place through the chi-square test, or Fisher's exact test, for categorical variables, and through the analysis of variance (ANOVA), or Kruskal-Wallis non-parametric test, for continuous quantitative variables.

The primary endpoint of the study, namely the percentage of patients with symptom improvement, will be statistically analyzed through a two-sided, considering the 10% non-inferiority margin established during the sizing phase of the study. The degree of improvement (pain expressed in NRS numerical scale, number of weekly bleeds) will be compared between groups through analysis of variance (ANOVA), or non-parametric Kruskal-Wallis test, with post-hoc evaluations of differences between groups. The satisfaction of the therapy, both in terms of cost and efficacy, will be compared between the study groups through the chi-square test, or Fisher's exact test. In a very similar way, secondary endpoints will be analyzed. For all statistical comparison, $p<0.05$ was considered significant.

Results

A total of 96 patients were evaluated in this trial. The study lasted 1 year. Patients were equally divided in the 3 treatment groups (32 per each group), and their characteristics at baseline did not differ from one group to the other. The average duration of symptoms before starting the study was similar in both groups (50 days for group 1, 48 for group 2 and 45 days for group 3). The average pain at rest and on evacuation evaluated with the VAS scale was 8, with no significant difference between the treatment groups. The bleeding evaluated on a scale from zero to 10 was 7 (table 1). During the second and third visit, a significant improvement of symptoms was observed in the groups 1 and 2 in respect to group 3. These data were statistically significant (Table 2). Both pain and bleeding were improved along during the treatment course (fig. 1 and fig 2).

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	Group 1 fito	Group 2 fito+	Group 3no fito	p value (significance obtained when p<0.05)
Patients	32	32	32	
Duration of symptoms (days)	50	48	45	0.2
Pain at rest (on a VAS scale)	8	8	8	1
Pain on evacuation(on a VAS scale)	8	8	8	1
Bleeding (episodes/week)	7	7	7	1
Size of the lesion (mm)	8	6	6	0.7

Table 1: Patients characteristics at baseline.

	Group 1 fito	Group 2 fito+	Group 3no fito	p value (significance obtained when p<0.05)
Patients	32	32	32	
Duration of symptoms (days)	50	48	45	0.2
Pain at rest (on a VAS scale)	8	8	8	1
Pain on evacuation(on a VAS scale)	8	8	8	1
Bleeding (episodes/week)	7	7	7	1
Size of the lesion (mm)	8	6	6	0.7

Table 2: Clinical results (symptoms improvement).

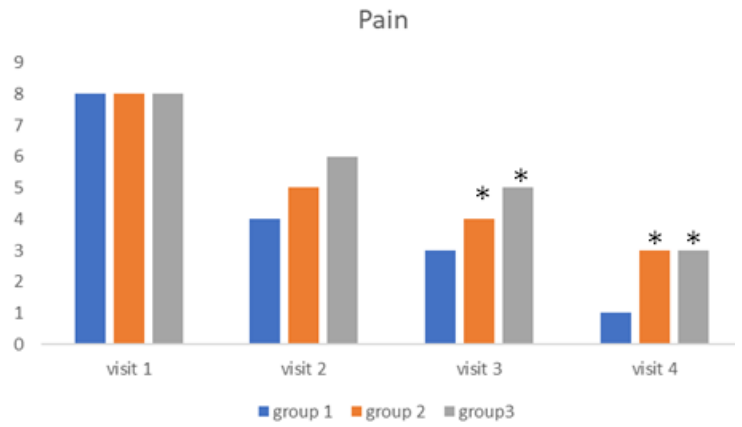

Figure 1: Pain (significance reached from visit 3 in group 2 and group 3 in comparison to group 1 (p<0.001 indicated as *).

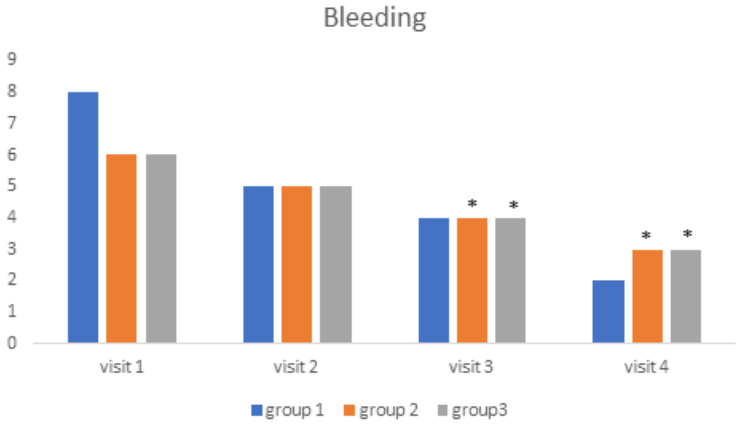

Figure 2: Weekly bleeds (significance reached from visit 3 in group 2 and group 3 in comparison to group 1 (p<0.001 indicated as *)

Patients satisfaction, including both efficacy and cost, expressed on a scale ranging from o to 10, was considered excellent (8.5) for group 1, good (7) for group 2 and on average (6) for group 3. Results indicated that patients were highly satisfied by the treatment with Fitostimoline® Proctogel in respect to the other treatments both in terms of efficacy and in terms of its costs. This data was statistically significant (p<0.0001, Table 3). Table 4 reports secondary outcomea: 1 only patient in group 3 needed a surgical intervention before the end of the study.

A pharmacoeconomic research was also performed, analyzing the prices of the products used in this trial as indicated in their technical files; the data obtained are reported in Table 5. There can be noticed a significant lower price for Fitostimoline® Proctogel in comparison to all the competitors. Furthermore, formats of products are similar; the cost was then calculated on a monthly basis, and after a 4 moths period of therapy. The cost of Fitostimoline® Proctogel is about 25% compared to other products, with a significant saving in terms of costs.

	Group 1 fito	Group 2 fito+	Group 3 no fito	P value (significance obtained when p<0.05)
Overall patient satisfaction	8.5	7	6	p<0.01

Table 3: Patient satisfaction.

	Group 1 fito	Group 2 fito+	Group 3 no fito	P value (significance obtained when p<0.0001)
Percentage of patients who required invasive therapies	0	0	3.125%	p<0.0001

Table 4: Percentage of patients who required invasive therapies and who reached complete healing.

Product	grams	Price (euros)	posology	Application price	Price/ month (60 applications)	Price for a 4 month period
Fitostimoline 35 g 10 euro	35	11	1	0.3	18.88	75.43
Antrolin 14,8 euro	30	16	2.5	1.3	80	320
Rectogesic 30g 73 euro	30	73.09	0.375	0.9	54.8175	219.27
Levorag 20 tubi 35.50 euro	20	32.6	3.5	1.63	97.8	391.2

Table 5: Cost evaluation.

Discussion

Anal fissure is a frequent disease that causes a significant reduction in patients QoL. An adequate management and treatment of acute anal fissure is needed to avoid the fistula chronicization and for improvement of the quality of life (QoL). In cases resistant to topical therapy, invasive therapies are possible such as injection of botulinum toxin, mechanical anal dilatation, diathermocoagulation of the fundus, injection of autologous fat, lateral internal sphincterotomy. However, all this therapeutic strategies are invasive and has a limited efficacy. Thus, it appears of upmost importance to investigate a primary, non invasive therapy. The treatment period is generally of 4 months and the therapies used are topic creams with a posology of two daily applications. This determines a large usage of the products, which will need to be bought by the consumers at least once per month. Despite the significant medical arsenal available today, the employment of Fitostimoline® proctogel (alone or in combination with other medications) has not been studied yet for anal fissure; the rationale of this study is to evaluate in a prospective, randomized, controlled way, symptoms improvement and overall patients satisfaction (primary endpoints) and the need for invasive interventions and complete healing of the fissure (secondary endpoint) using Fitostimoline® proctogel with or without other topical aids available on the market, in particular Levorag®, Antrolin® or Rectogesic®. A pharmaco-economic evaluations is also scheduled. The aim of the present study is the search for a drug which is at the same time effective and cheap. A prospective randomized trial was conducted, including 96 patients evaluated more times by 3 surgeons, and cathegorized according to a data recording sheet including data about symptoms and macroscopic appearance. The results of the present study demonstrate that utilizing Fitostimoline® proctogel, alone or in combitation with other oinments, allows for a good performance in terms of symptoms improvement and fissure healing; especially this ointment - alone or in combination with other topic medication - shows non inferior results when compared to standard topic therapy for anal fissure.

The most relevant problem of fissures is represented by pain, independently on the fissure dimensions. This parameter was significantly reduced in the group of patients treated with Fitostimoline® proctogel both alone and in association in respect to the other treatment group. This activity could be explained by the regenerating and anti-inflammatory properties of the analyzed

device. These data were also corroborated by the clinical efficacy of the analyzed device in terms of pain and fissure dimensions. Even if in this trial the products were given for free to the enrolled patients, a pharmacoeconomic analysis was performed. All the patients treated with Fitostimoline® proctogel indicated that in relation to its efficacy, the product has a very good cost-efficacy relation. All the patients treated with Fitostimoline® proctogel considered the treatment affordable while the combinations or the alterative products were considered too expensive for a chronic treatment like the one examined in this trial.

Conclusions

The results of this study indicate that Fitostimoline® proctogel could be a new efficacious and economic tool which can be used for the treatment of fissures. This lead us to the conclusion that we have a new, highly tolerated and efficacious device which gives advantages also from a pharmacoeconomic point of view for the patients treatment.

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