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Management of Chronic Anal Fissure with a Novel Topical Hemp-Herbal-Based Ointment: A Pilot Study

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Keywords
Anal fissure · Cannabinoid treatment · Surgery · Clinical trial · Analgesia

Abstract
Introduction: Anal fissure (AF) is a common anorectal disease. Although several pharmacological treatments are available, many patients still require surgical interventions. In this study, we aimed to evaluate the efficacy of an ointment based on a multifunctional blend of herbal ingredients including hemp (ProctoFiz) for chronic AF. ***Methods:*** A single-arm, questionnaire-based prospective study was conducted in a large tertiary center to evaluate the outcomes of patients suffering from chronic AF treated with topical ProctoFiz. ***Results:*** Ninety-two patients were included in the study, 54 (58.7%) were females with a median age of 39 (range 17–78). 32 patients (34.7%) suffered from recurrent AF before enrolling in the study, and 5 patients (5.4%) underwent previous surgical interventions for AF. Three patients (3.2%) were lost to follow-up, leaving 89 patients for analysis. Eighty patients (89.9%) reported significant improvement of symptoms after 1 week using ProctoFiz, and 79 patients reported continued improvement after 1 month of treatment. The mean pain Visual Analog Score (VAS) declined by 6.6 points (8.9 vs. 2.3; 95% CI: 7.20 to −5.99, $p < 0.0001$) following 1 week of treatment, with continuous improvement to a mean of 0.64 after 1 month. Negative impact on quality of life significantly decreased from a mean of 8.8 to 0.38 following a month of treatment ($p < 0.0001$), with significant reduction in the number of patients suffering from bleeding following bowel movements (64.1–2.5%; $p = 0.0001$). ***Conclusion:*** Hemp-based topical treatment of AF is feasible and significantly improves AF-correlated symptoms.

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Introduction

Anal fissure (AF) is one of the most painful anal disorders and has a negative impact on the patient's quality of life (QoL). AF is a linear crack or tear in the squamous epithelium of the lower half of the anal canal, usually extending from below the dentate line to the anal verge. AF is painful because of sensory innervations in this area. Fissures occur in all age groups, with equal prevalence in men and women. Possible causes of AF include infection

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and traumatic injury to the anal canal such as from passage of hard stool or severe diarrhea [1], although some studies also suggest that ischemia of the anal canal plays an important role in the pathogenesis of AF [2]. Atypical AFs may develop in people with Crohn's disease, sexually transmitted diseases, tuberculosis, postsurgical local trauma, anal intercourse, anal cancer, or chemotherapy [2].

AF can be acute or chronic. Acute AF is a simple rupture in the anoderm existing for less than 2 months, whereas chronic AF is present for more than 6–8 weeks. The latter is characterized by exposed fibers of internal anal sphincters at the base, hypertrophied proximal anal papilla, and a distal skin tag or sentinel pile.

Both acute and chronic AFs are associated with anal pain, spasm, and/or bleeding upon defecation. In the past, surgical treatment of AF was the treatment of choice in order to lower the resting anal pressure. Historically, these procedures included anal dilatation, nowadays obsolete due to poor functional results, and lateral sphincterotomy [3, 4].

Currently, initial treatment of AF consists of administration of various medications and local ointments. They include topical agents such as calcium channel blockers and topical nitroglycerin along with laxatives and topical anesthetic creams [5]. These have gained popularity mainly because they enable early intervention and are considerably cheaper compared to surgical intervention [6]. The principal goal is to relieve symptoms by reducing anal muscle contractility and spasm. This decreases the risk of repeated trauma upon defecation. In addition, injection of botulinum toxin has achieved good results, although repeated injections may be required [7]. Finally, in patients without an adequate response to medical treatment, lateral sphincterotomy of the internal sphincter may be necessary. This procedure achieves high rates of therapeutic success; however, many patients experience significant changes in continence following surgery, ranging from almost 45% in the immediate postoperative period to 1–8% on long-term follow-up [8, 9]. There are a number of contributing factors to this phenomenon, including the rectal reservoir capacity, rectal sensation capacity, and the consistency of stool, which may compensate for the trauma to the sphincter muscles. However, since these factors are highly variable among patients, it is difficult to predict which patients will suffer from long-term incontinence that can be devastating for their QoL. These outcomes must be taken into consideration when offering surgical intervention [10].

A proprietary multifunctional herbal-based product for topical application has been developed, consisting of natural ingredients, each of which targets a specific pathophysiological mechanism of the disease. For example, to counteract the increase in vascular pressure and ischemia, lowering of resting pressure is achieved by one component with a vasodilatory effect, while other herbal ingredients provide anti-inflammatory and analgesic effects. Another ingredient acts as a bio-adhesive, aimed at protecting and healing the fissure wound. The product, ProctoFiz© (by ESPA Biomedical Ltd., Ramat Hasharon, Israel) is currently an over-the-counter cosmetic product, which has been approved as a medical device by the Israeli Ministry of Health. ProctoFiz© contains the following ingredients: hemp seed oil, calendula, sweet almond, myrtle, arnica, and seaweed extract. We report the clinical outcomes in this prospective questionnaire-based study of patients with chronic AF treated with this novel herbal-based natural product.

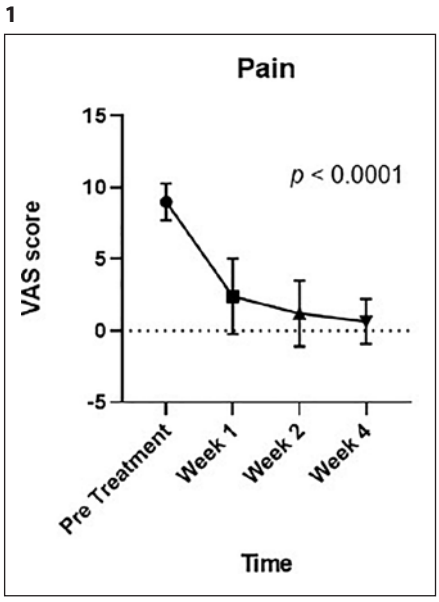
Methods

Study participants were adult patients suffering from chronic AF, diagnosed over a period of 18 months by a single senior colorectal surgeon (ER) at an ambulatory colorectal specialty clinic. We included patients presenting with anal pain, which was clinically determined to be associated with a midline (dorsal or ventral) AF for a minimum of 1 month. All study subjects volunteered to participate in the study and each signed an informed consent. The study was approved by the Institutional Review Board (Helsinki Committee) of Sheba Medical Center. All research was performed in accordance with IRB regulations according to the Declaration of Helsinki. We excluded patients with inconclusive diagnosis of AF or with other chronic conditions, such as inflammatory bowel disease or known immunodeficiencies.

After an initial screening visit, when a baseline questionnaire was given to participants in order to assess their pretreatment clinical status, patients were treated with ProctoFiz applied to the external anal area three to four times daily for a period of 1 month. In addition to the topical treatment, all patients were instructed to use laxatives and dietary supplemental fiber.

One week following the initiation of treatment, interviewers (research assistants that had never met the patients nor had they participated in the design of the questionnaire or the analysis of the results) used a telephone questionnaire, which included questions to evaluate the impact of the symptoms on the patient's QoL using Visual Analog Scale (VAS) for pain. Answers used a scale from "0" to "10," with "10" signifying the highest negative impact. Additional symptoms were evaluated, including anal bleeding and burning sensation. Patients were telephoned and interviewed a second time, 2 weeks after the initiation of treatment.

At 1 month after the screening visit, a third in-person follow-up was scheduled, during which a clinical evaluation was performed. Patients with no subjective relief at 1 month were referred to be evaluated for further medical treatment or surgery.



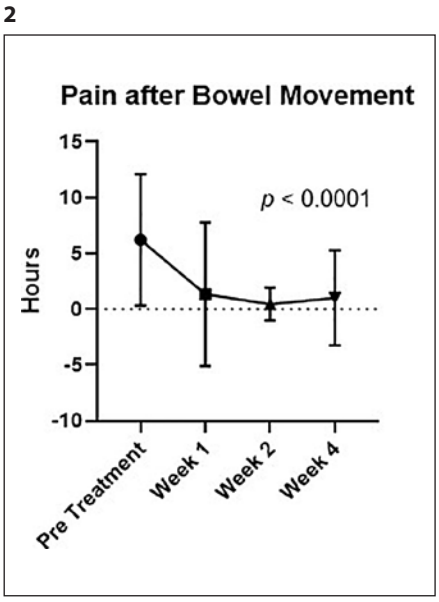


Fig. 1. Visual Analog Score (VAS) assessment of pain from AF prior to treatment and at follow-up of 1, 2, and 4 weeks.
Fig. 2. Assessment of the duration of pain following bowel movement in patients with AF prior to treatment and at follow-up of 1, 2, and 4 weeks.

Product Details

ProctoFiz is an over-the-counter ointment that consists of a blend of herbal extracts designed to act on the various pathophysiological mechanisms associated with AF. The product primarily includes hemp seed oil that acts as an analgesic and anti-inflammatory [11], tocopherol that induces local vasodilatation, and various other ingredients such as *Arnica montana* flower oil and marine algae extract that have a calming effect on inflamed skin and reduce inflammation [12, 13].

Statistical Analysis

Statistical analysis was performed using SAS/STAT software (version 9.4 by Statistical Analysis System Corporation, North Carolina, USA). Data were compared using Fisher's exact test and χ^2 to evaluate differences between qualitative variables and using a *t* test to compare quantitative variables. One-way ANOVA was used to determine statistically significant differences between the means of three or more groups. A *p* value of <0.05 based on a two-tailed analysis was considered significant.

Results

Out of 102 patients found eligible to participate in the study, 10 patients declined to participate, leaving 92 patients eligible to participate in the study, 54 (58.7%) of which were female. Median age was 39 years (range 17–78). Eighty-nine (96.8%) patients suffered from constipation with anal pain and difficulties with defecation. Mean duration from the beginning of symptoms to the screening visit was 20 weeks (range 4–96 weeks). Sixty patients (65.3%) were diagnosed with AF at the initial visit or were referred by a family practitioner to our proctology clinic with complaints suggesting AF. Thirty-two (34.7%) patients suffered from recurrent symptomatic events before enrolling in the study and were previously treated with topical CCBs and topical analgesics. None of the patients were previously treated with Botox injections, and 5 (5.4%) patients had previously underwent lateral sphincterotomy for AF. Three (3.2%) patients were lost to follow-up (two did not answer the telephone and one did not appear for the follow-up visit), leaving 89 patients for final analysis. Median follow-up was 30 days (range 7–76 days).

After 1 week of treatment with ProctoFiz©, 80 (89.9%) patients reported a significant improvement of symptoms: a significant reduction in pain and/or anal bleeding. After 1 month of treatment, 79 patients reported continued improvement. Regarding side effects, 2 (2.2%) patients complained of headaches 1 week after initiation of treatment, which resolved the following week. Seven patients did not report any improvement in their symptoms. Six patients were treated with topical nifedipine. Of these patients who were treated with nifedipine, 3 patients were eventually referred for surgical intervention (lateral sphincterotomy) due to failure of medical therapy.

Symptomatic improvement following 1 week of treatment was demonstrated by a statistically significant decrease in the mean VAS pain score: from 8.9 to 2.3 – a total of 6.6 points (95% CI: 7.20 to −5.99, $p < 0.0001$). At the 1-month follow-up visit, continued improvement in anal pain was seen with a mean VAS score of 0.64 (Fig. 1). Furthermore, in patient reports after 1 week of treatment about the length of time of pain and/or discomfort fol-

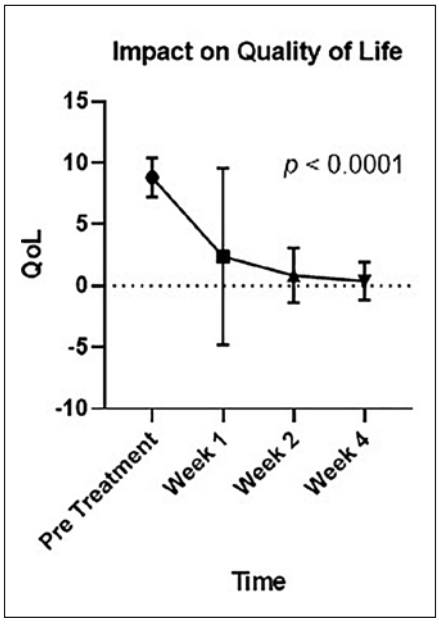


Fig. 3. Evaluation of the impact by symptoms on quality of life (QoL), in patients with AF prior to treatment and at follow-up of 1, 2, and 4 weeks.

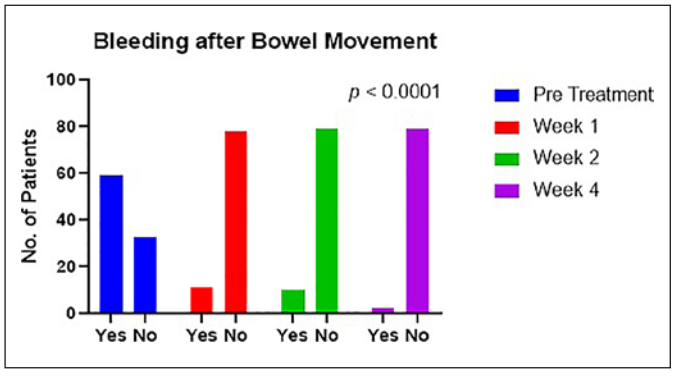


Fig. 4. Number of patients with AF suffering from anal bleeding, related to defecation prior to the initiation of treatment, and at follow-up of 1, 2, and 4 weeks.

lowing a bowel movement, a significant decrease was noted, from a mean of 6.2 to 1.34 h. Patients reported a decrease in duration of pain after a bowel movement after using the ointment for 2 weeks, with a slight increase in duration of pain between 2 weeks and 1 month (mean 0.45–1.01 h) (Fig. 2). Overall, patients reported a decrease in the negative impact of their symptoms on their QoL, with a statistically significant decrease from a mean of 8.8

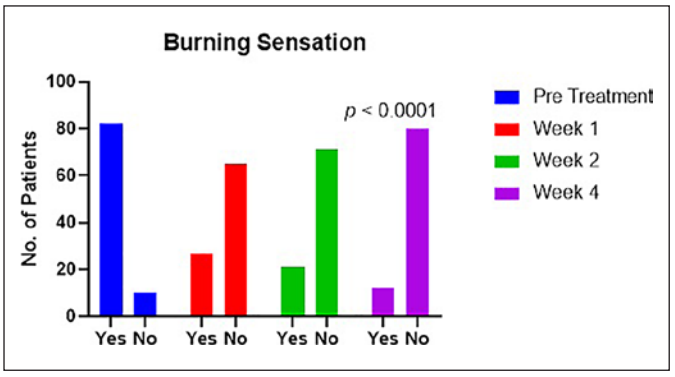


Fig. 5. Number of patients with AF suffering from burning sensation prior to treatment and at follow-up of 1, 2, and 4 weeks.

to 0.38 following 1 month of treatment ($p < 0.0001$) (Fig. 3).

Fifty-nine (64.1%) patients suffered from anal bleeding following bowel movements prior to the initiation of treatment. After 1 week of treatment, 11 (12.4%) patients continued to suffer from bleeding associated with bowel movements. At 1 month of follow-up, only 2 patients (2.2%) suffered from anal bleeding (Fig. 4). In addition, the number of patients who complained of anal burning sensation following bowel movement decreased from 82 (89.1%) patients at initial screening to 27 (29.4%) patients at 1 week and 12 patients (13.1%) at 1 month of treatment (Fig. 5).

Discussion

AF is one of the most common causes of anorectal pain and discomfort, often accompanied by a burning sensation and bleeding after defecation. In many patients, the initial tear in the anoderm causes a vicious cycle of persistent pain, as many of these patients try to defer defecation due to the associated pain [2]. The mainstay of treatment for AF aims to break this vicious cycle, to ease defecation by reducing anal sphincter spasm and pressure in the area, thus preventing additional trauma to the anal mucosa and promoting healing of the fissure [14].

Therapeutic options for patients suffering from chronic AF are divided into pharmacological treatments and surgical intervention. Although it is estimated that around 35% of patients will spontaneously heal for a brief period, recurrence is quite common [4]. Surgical intervention, although proven to be the most effective method of treatment, should be offered to patients only after pharmacological treatment has failed because it carries a signifi-

cantly higher risk of anal incontinence, severely impacting the patient's QoL. For this reason, patients are generally first given a trial of local treatment with ointments containing topical nifedipine or nitroglycerin, both vasodilators that reduce the muscle spasm of the anal sphincter [15]. However, side effects of these medications are quite common and include hypotension, headaches, and dizziness.

In this study, we report the initial results of a single-arm pilot study of patients with chronic AF treated with a novel herbal-based natural ointment, ProctoFiz©. Although our study lacks a control group and has a fairly limited time period for follow-up, the results are encouraging as almost 90% of patients reported significant improvement or complete resolution of their symptoms after 1 month of treatment. This significant improvement in the patients' symptoms is similar to reported outcomes in standard topical agents including nitroglycerin and calcium channel blockers standing at 48–92% [16]. Of particular note is that the maximal or most significant effect of using the ointment in most patients was observed after only 1 week of treatment and that the rate of side effects is considerably low in our study.

The positive results in this study were achieved using ProctoFiz as the therapeutic agent in conjunction with standard directives regarding stool softeners and dietary advice. We believe that the multifunctional composition of this product effectively addressed the underlying causes of AF. Standard conventional medications usually target one mechanism for healing: lowering anal pressure through vasodilation by blocking the calcium channel. ProctoFiz is a product with a mix of herbal components that advantageously act with multiple mechanisms to achieve superior efficacy for vasodilation, lubrication, wound protection, pain relief, and anti-inflammatory effect. For example, *Calendula*, one of the ingredients in ProctoFiz, has been reported as a possible remedy for recurrent AF. In a case report by Naseer et al. [17], published a decade ago, a woman with recurrent AF used marigold *Calendula* oil a few times a day with complete resolution of symptoms. Although the exact mechanism of action is unclear, *Calendula* was shown to promote wound healing by enhancing fibroblast activation and migration, increasing the production of granulation tissue [18].

Hemp seed oil, a good source of cannabidiol, which is used in various clinical scenarios, has recently gained increasing popularity, with the legalization of its use for medical purposes around the world, mainly as an analgesic. The advantages of CBD were recently summarized in a meta-analysis that investigated its current use in medicine. CBD was associated with significant reduction of pain and spasticity, along with a reduction in nausea and vomiting due to chemotherapy [19]. When used topically, CBD can also induce vasodilatation through CB1 receptors, thus reducing local ischemia, promoting wound healing. A recent abstract presented at the annual meeting of American college of gastroenterologists in 2020 described 4 patients treated with topical CBD (1.4–2 mg/g twice daily). All patients reported improvement within a few days, with no side effects [20].

The main limitation of our study was the single-arm design with the lack of a control group. Although our results are encouraging, especially considering the fast response to treatment in the majority of patients, the lack of comparison to patients treated with placebo or to standard treatments obligates us to take these results with necessary caution. Another caveat of our study is the fairly short follow-up period. Furthermore, the short follow-up negates the possibility to properly assess fissure recurrence or complete wound healing, which can take several months. However, in our experience, most patients with a fissure are not followed up for a long period, and we believe that a shorter follow-up represents real-life experience. The high success rate of eliminating symptoms suggests that topical application of the novel herbal-based product ProctoFiz can be considered as an effective and safe nonsurgical method for short-term management of chronic AF. In addition, we believe that this alternative should be considered in patients who develop significant side effects from standard treatments for AF. Further comparative studies are needed to determine whether this treatment could be considered as a first-line treatment for relief of symptoms and healing of AF.

Statement of Ethics

This study protocol was reviewed and approved by the Institutional Review Board of the Sheba Medical Center, approval number, 7490-20SMC. Written informed consent was obtained from participants to participate in the study.

Conflict of Interest Statement

The authors declare that they have no conflict of interest.

Funding Sources

No funding was received for this study.

Author Contributions

Study conception and design – Edward Ram, Yaniv Zager, and Nir Horesh. Acquisition of data – Edward Ram, Nir Horesh, Raanan Meyer, and Samia Joubran. Analysis and interpretation of data – Nir Horesh, Edward Ram, Dan Carter, Raanan Meyer, and Yaniv Zager. Drafting of the manuscript – Edward Ram, Nir Horesh, and Samia Joubran. Critical revision of the manuscript – Nir Horesh, Edward Ram, Dan Carter, Yaniv Zager, Samia Joubran, and Raanan Meyer.

Data Availability Statement

The datasets generated during the current study are not publicly available but will be available from the corresponding author on reasonable request.

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