Increasing efficacy and reducing side effects in treatment of chronic anal fissures

A study of topical diazepam therapy

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Abstract
This is a single institution nonexperimental study intended to analyze the therapeutic efficacy of topical diazepam in treating symptoms of chronic anal fissures.

Anal fissures are a common cause of anal pain. Conventional treatments include nonsteroidal anti-inflammatory drugs, topical creams, such as nitroglycerin and nifedipine, and surgery. However, these treatments are usually suboptimally efficacious or have deterring side effects.

Patients at an outpatient community center with a diagnosis of a chronic anal fissure were prescribed either topical 2% (n = 19) or 4% (n = 18) diazepam cream between January 2013 and February 2015. We retrospectively analyzed their responses to treatment.

All 19 patients using 2% diazepam cream experienced a positive response in pain, whereas 47.4% experienced a complete response, with a numerical rating scale (NRS) score of 0 (0–10). Eighty-eight percent of patients using 4% dose had a positive response in pain, whereas 23.5% experienced a complete response. Ninety-four percent of patients using 2% dose had a positive response in anal bleeding, whereas 68.8% experienced a complete response with an anal bleeding score (ABS) of 2 (2–9). Ninety-four percent of patients using 4% dose had a positive response in anal bleeding, whereas 64.7% experienced a complete response. Only 1 patient reported a side effect from diazepam cream—perianal pruritus.

Both 2% and 4% topical diazepam provided significant pain and bleeding relief from chronic anal fissures that were refractory to conventional therapies. There were insignificant differences when assessing independent comparisons for pain and bleeding between the doses.

Abbreviations: ABS = anal bleeding score, NRS = numerical rating scale.

Keywords: anal, benzodiazepine, cream, diazepam, fissure, pain, topical

1. Introduction

Anal fissures are one of the most common anorectal disorders. We define a chronic anal fissure as a symptomatic anal fissure that has persisted without any relief for greater than 6 weeks.\textsuperscript{[1]} Patients classically present with anal pain and bleeding. Young and middle-aged adults are primarily affected with no gender predilection. Although many cases are benign, symptoms can be debilitating and leave patients with a significantly reduced quality of life.\textsuperscript{[2]}

External anal sphincter defects that are associated with anterior fissures, along with hypertonia or spasm of the internal anal sphincter in most fissures, have been recognized as factors of fissure pathogenesis.\textsuperscript{[3,4]} Manometry studies have demonstrated significantly higher pressures of the internal anal sphincter.\textsuperscript{[5,6]} Additionally, the posterior midline of the anal canal is poorly perfused and increased internal sphincter pressure further reduces blood flow. With decreased perfusion to the anal canal, the anal fissure heals slowly, if at all, as the inciting events continue; this leads to fissure nonhealing, defining it as chronic, unless intervention occurs.

Initial therapy consists of increasing dietary fiber and using sitz baths. Topical agents—anesthetics, vitamins, and anti-inflammatories—treat refractory cases. Treatments aimed at reversible inhibition of anal sphincter spasms are often required for chronic cases and include topical nitroglycerin,\textsuperscript{[7]} nifedipine,\textsuperscript{[8]} and diltiazem\textsuperscript{[9]} cream. Unfortunately, treatment response is often sub-optimal and can lead to poor patient compliance.\textsuperscript{[10]} Diazepam is a benzodiazepine commonly used to treat anxiety. In addition, it acts centrally to relax striated muscles. A rectal formulation has been made available for prolonged seizures.\textsuperscript{[11]} The primary aim of our study was to determine if a topical

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diazepam cream could provide immediate and short-term symptomatic relief from chronic anal fissures. Our secondary aims were to analyze the time from cream usage to symptom relief, determine adverse effects, and measure patient satisfaction.

2. Materials and methods

2.1. Study design and objective

This was a single institution nonexperimental study of therapeutic efficacy of topical diazepam cream in treating anal pain and bleeding associated with chronic anal fissures. Symptomatic relief was chosen as the end point, since the primary benefit of using topical creams is subjective symptoms relief rather than actual healing of the fissure. The study protocol was reviewed and approved by Mercer University’s institutional review board and ethics committee prior to gathering data. Informed consent was obtained from all study subjects.

2.2. Cream information

The diazepam cream in this study was produced by Graves Pharmacy (770 Pine St #100, Macon, GA). The product was made in-house by compounding pure diazepam and a standard emollient cream base to form 2% and 4% diazepam cream. Each 30g 2% and 4% diazepam cream tube is priced at $39.40 and $44.10, respectively. Patients were instructed to dispense a pea-sized amount of cream on their fingertip and apply a thin film on their clean anoderm 3 times a day.

Diastat dispensers deliver 20 mg of diazepam per application to the simple columnar epithelium of the rectum for an adult dose.[12] This results in 90% absolute bioavailability[12] and accounts for the systemic therapeutic effect seen in status epilepticus.[13] To lower the likelihood of toxicity, we chose the maximum dose (4%) to deliver approximately ½ of the recommended Diastat dose, given that our study’s recommended pea-sized dose per application is ~300 mg (4% of 300 mg cream = 12 mg diazepam). A lower dose, 2%, was chosen to be ½ of our original dose to compare therapeutic effects while further decreasing the likelihood of side effects.

2.3. Patients

Men and women over the age of 18, excluding those with significant mental impairment requiring inpatient treatment and inflammatory bowel diseases, who were prescribed either 2% or 4% diazepam cream at Gastroenterology Associates of Central Georgia (610 Third Street, Macon, GA) between January 2013 and February 2015 qualified to participate in the study. These 37 patients were previously diagnosed with a single anal fissure that became refractory to conventional treatment. Patients were initially contacted via phone call to request permission for participation in our study. Informed consent with detailed information of the study protocol was then obtained from interested patients.

All subjects’ charts were retrospectively reviewed for the following baseline patient characteristics at the time of initial cream use: age, sex, race, specific symptoms at time of prescription, etiology of anal symptoms, gastrointestinal comorbidities, duration of symptoms prior to cream usage, previous treatments, side effects from prior treatments, and date of cream use. Follow-up data was acquired by subsequent phone calls.

2.4. Outcome measures

The primary end points of our study were absolute change from baseline in patient-reported pain and bleeding intensity. Pre- and post-diazepam cream anal pain was measured using an oral numerical rating scale (NRS)[14] (0–10), with 10 indicating most severe pain and 0 indicating absence of pain. Unidimensional pain scales such as the NRS have been validated as reliable measures of acute pain.[15] Bleeding was graded using an anal bleeding score (ABS), which was modified from the Rectal Bleeding Score created by Takemoto et al.[16]; the sum of the frequency score and the amount score is proposed to evaluate the grade of bleeding. The frequency score was evaluated as: score 5, >5 bleeding episodes per week; score 4, 3 to 4 episodes per week; score 3, 1 to 2 episodes per week; score 2, 1 to 2 episodes per 2 weeks; and score 1, <1 episode per 2 weeks. The amount score was evaluated as: score 4, severe (blood visible on stool); score 3, moderate (blood streak on toilet paper); score 2, mild (blood spot on toilet paper); and score 1 (nonexistent). Additionally, patient satisfaction was determined using a standard numerical scale (1–5), with 5 indicating highest satisfaction and 1 indicating no satisfaction. The recorded NRS and ABS values reflected patients’ symptoms at the time of follow-up phone calls.

2.5. Statistical analysis

Descriptive statistics were generated to assess the characteristics of subjects. Means and standard deviations or medians and interquartile ranges were reported for continuous variables, and frequencies and proportions were reported for categorical variables. The Wilcoxon-Signed Rank test was used to make dependent comparisons with the absolute change from baseline in patient-reported anal pain and bleeding intensity for each dosage and overall. The Wilcoxon rank-sum test was used to make independent comparisons with the same parameters between the 2 dosages. A 2-tailed test was used for each test, and a p-value less than 0.05 was used to determine statistical significance. Medians with interquartile ranges, frequencies, and proportions were reported to measure responses to symptom relief and cream use. SAS version 9.4 (SAS Institute, Cary, NC) was used for all analyses.

3. Results

We identified 37 patients who met our study criteria and elected to participate. Descriptive characteristics of subjects are reported overall and by dose percentage in Table 1. Of the 37 patients using the diazepam cream, 19 received the 2% dose and 18 received the 4% dose. The overall mean age of patients was 51 years; mean ages of patients using the 2% and 4% cream were 54 and 49 years, respectively. Thirty-six (97.3%) subjects overall presented with anal pain, whereas 33 (89.2%) elected to participate. Descriptive characteristics of subjects are reported overall and by dose percentage in Table 1. Of the 37 patients using the diazepam cream, 19 received the 2% dose and 18 received the 4% dose. The overall mean age of patients was 51 years; mean ages of patients using the 2% and 4% cream were 54 and 49 years, respectively. Thirty-six (97.3%) subjects overall presented with anal pain, whereas 33 (89.2%) presented with anal bleeding. The numerical rating scale range for overall pain before diazepam cream treatment was 3–10 (max—10), and the range for overall anal bleeding scores was 2–9 (max—9). Anal pain was present in all patients using the 2% dose and 17 (94.4%) patients using the 4% dose. Eighty-four percent of the 2% group and 94.4% of the 4% group experienced anal bleeding. No patients reported relevant comorbidities.

The median duration of symptoms prior to an office visit was 3.0 months overall, 3.0 months in the 2% group, and 2.0 months in the 4% group (Table 1). The mean duration of patient...
follow-up following diazepam cream use was 7.8, 7.8, and 7.9 months for the overall cohort, 2%, and 4% groups, respectively.

All 37 subjects were on other medications during diazepam cream therapy and these medications were checked for drug interactions using Epocrates. Table 2 summarizes these findings. Six drugs, including sertraline and omeprazole, inhibit hepatic metabolism of diazepam; none of the patients reported symptoms of systemic toxicity such as sedation. However, it is impossible to exclude the possibility that some inhibition of metabolism occurred without obtaining metabolite levels. One drug—butalbital—induces hepatic metabolism of diazepam; the 1 patient on butalbital responded well to the diazepam cream and had already discontinued therapy by the time of follow-up. Twenty different drugs cause additive effects with concurrent diazepam cream usage, which increases the likelihood of sedation and psychomotor impairment; none of these patients reported these side effects. Four drugs—all opioids—cause more severe additive effects, with additional increased likelihood of vasodilation and hypotension; none of these patients reported these side effects.

Use of diazepam cream resulted in a statistically significant improvement of anal pain and bleeding (Table 3). The median differences in pre- and post-treatment NRS scores were positive and measured to be 7.0 for the 2% dose, 4.0 for the 4% dose and 5.0 overall (all $P < .0001$). For anal bleeding, the median difference in ABS were also positive and measured to be 3.5 for the 2% dose, 2.0 for the 4% dose, and 3.0 overall (all $P < .0001$). Overall NRS scores decreased from a median of 8.0 before treatment to a median of 2.0 after treatment (Table 3, Fig. 1A). The results were similar for the 4% group; however, in the 2% group, the scores decreased from a median of 8.0 before treatment to 1.0 after cream use. Anal bleeding scores decreased from an overall median of 6.0 to 2.0 following treatment (Table 3, Fig. 1B). The results were similar for the 4% group, but the median score before treatment in the 2% group was slightly higher at 7.0 and decreased to 2.0 after cream use. There were no statistical differences between the 2% and 4% doses when assessing independent comparisons for anal pain (Fig. 2A) and bleeding (Fig. 2B); however, there was a non-significant trend for the median difference in NRS scores to be greater for the 2% dose.

Table 2

| Characteristic                               | Overall (N=37) | 2% Cream (N=19) | 4% Cream (N=18) |
|----------------------------------------------|----------------|-----------------|-----------------|
| Age in years, mean, SD                        | 51.3 (± 13.8)  | 53.8 (± 12.2)  | 48.6 (± 15.1)  |
| Race, n, %                                    |                |                 |                 |
| White                                        |                |                 |                 |
| Black                                        |                |                 |                 |
| Other                                        |                |                 |                 |
| Baseline anal pain Present, n, %              | 36 (97.3)      | 19 (100.0)      | 17 (94.4)       |
| Baseline anal Bleeding present, n, %          | 33 (89.2)      | 16 (84.2)       | 17 (94.4)       |
| Duration of symptoms prior to office visit, months, median, IQR | 3.0 (1.5–8.0)  | 3.0 (2.0–11.0)  | 2.0 (1.5–5.0)  |
| Follow-up time, months, mean, SD             | 7.8 (± 3.8)    | 7.8 (± 4.1)     | 7.9 (± 3.7)     |
| Frequency of cream application, n, %          |                |                 |                 |
| Once a day                                    | 3 (8.1)        | 3 (15.8)        | 0 (0)           |
| Twice a day                                   | 22 (59.5)      | 12 (63.2)       | 10 (55.6)       |
| Three times a day                             | 10 (27.0)      | 4 (21.1)        | 6 (33.3)        |
| Four times a day                              | 2 (5.4)        | 0 (0)           | 2 (11.1)        |

IQR = interquartile range, SD = standard deviation.

Table 1

Descriptive characteristics of patients who experienced an anal fissure and received diazepam cream for symptoms of anal pain and bleeding.

| Characteristic                               | Overall (N=37) | 2% Cream (N=19) | 4% Cream (N=18) |
|----------------------------------------------|----------------|-----------------|-----------------|
| Age in years, mean, SD                        | 51.3 (± 13.8)  | 53.8 (± 12.2)  | 48.6 (± 15.1)  |
| Race, n, %                                    |                |                 |                 |
| White                                        |                |                 |                 |
| Black                                        |                |                 |                 |
| Other                                        |                |                 |                 |
| Baseline anal pain Present, n, %              | 36 (97.3)      | 19 (100.0)      | 17 (94.4)       |
| Baseline anal Bleeding present, n, %          | 33 (89.2)      | 16 (84.2)       | 17 (94.4)       |
| Duration of symptoms prior to office visit, months, median, IQR | 3.0 (1.5–8.0)  | 3.0 (2.0–11.0)  | 2.0 (1.5–5.0)  |
| Follow-up time, months, mean, SD             | 7.8 (± 3.8)    | 7.8 (± 4.1)     | 7.9 (± 3.7)     |
| Frequency of cream application, n, %          |                |                 |                 |
| Once a day                                    | 3 (8.1)        | 3 (15.8)        | 0 (0)           |
| Twice a day                                   | 22 (59.5)      | 12 (63.2)       | 10 (55.6)       |
| Three times a day                             | 10 (27.0)      | 4 (21.1)        | 6 (33.3)        |
| Four times a day                              | 2 (5.4)        | 0 (0)           | 2 (11.1)        |

IQR = interquartile range, SD = standard deviation.

Table 2

Patient’s concurrent medications’ interactions and potential effects with diazepam[17].

| Drugs                                      | No. of patients with concurrent use | Potential interactions with diazepam | Potential effects | No. of patients who reported effects |
|--------------------------------------------|-------------------------------------|--------------------------------------|------------------|-------------------------------------|
| Clopidogrel, cyclosporine, esomeprazole, omeprazole, sertraline, verapamil | 13 | Inhibits diazepam metabolism | Sedation, respiratory depression, psychomotor impairment | 0 |
| Butalbital                                 | 1 | Increase metabolism of diazepam | Decrease response to therapy | 0 |
| Alprazolam, amitriptyline, asenapine, carisiprodol, cetirizine, chloridiazepoxide-clidinium, chlorpromazine, clonazepam, cyclobenzaprine, doxepin, gabapentin, melatonin, methocarbamol, metoclopramide, pramipexole, promethazine, tizanidine, tramadol, trazodone, zolpidem | 36 | Additive effects | Increased likelihood of sedation, respiratory depression, psychomotor impairment | 0 |
| Fentanyl, hydromorphone-acetaminophen, morphine, oxycodone | 9 | More severe additive effects | Increased likelihood of sedation, respiratory depression, psychomotor impairment, vasodilation, hypotension | 0 |
There were no statistical differences in the median pre- and post-treatment scores between dosages. The majority of patients experienced a positive response in anal pain and bleeding following treatment (Table 4). Of the 36 patients with anal pain, 34 (94.4%) had a positive response; 13 (36.1%) demonstrated a complete response, reporting an NRS score of 0. All 19 patients using the 2% cream experienced a positive response to pain, with 47.4% developing a complete response. Fifteen (88.2%) of the 17 patients using the 4% cream demonstrated a positive response to pain and 4 (23.5%) developed a complete response, with an NRS of 2. The median time to improvement of anal pain was 7.0, 7.0, and 3.0 days for the overall, 2%, and 4% cohorts respectively. Thirty-one (93.9%) overall patients with anal bleeding experienced a positive response, and 22 (66.7%) developed a complete response. Fifteen (93.7%) patients in the 2% cohort had a positive response.

**Table 3**

| Symptom         | Pre-cream score median (IQR) | Post-cream score median (IQR) | Difference in scores median (IQR) | P  |
|-----------------|-----------------------------|-------------------------------|-----------------------------------|-----|
|                 | NRS                         |                               |                                   |     |
| Overall (n=36)  | 8.0 (7.0–10.0)              | 2.0 (0.0–4.0)                 | 5.0 (3.5–8.0)                    | <.0001 |
| 2% cream (n=19) | 8.0 (8.0–10.0)              | 1.0 (0.0–5.0)                 | 7.0 (4.5–8.0)                    | <.0001 |
| 4% cream (n=17) | 8.0 (5.0–9.0)               | 2.0 (1.0–3.0)                 | 4.0 (3.0–6.0)                    | <.0001 |
|                 | ABS                         |                               |                                   |     |
| Overall (n=33)  | 6.0 (5.0–8.0)               | 2.0 (2.0–3.0)                 | 3.0 (1.0–4.0)                    | <.0001 |
| 2% cream (n=16) | 7.0 (5.5–8.0)               | 2.0 (2.0–3.5)                 | 4.0 (2.0–6.0)                    | <.0001 |
| 4% cream (n=17) | 6.0 (3.0–6.0)               | 2.0 (2.0–3.0)                 | 2.0 (1.0–4.0)                    | <.0001 |

ABS = anal bleeding score, IQR = interquartile range, NRS = numerical rating scale.

*Derived from the Wilcoxon-signed rank test.

**Figure 1.** Overall changes in scores for anal pain (A) and anal bleeding (B). Circles represent medians and bars represent interquartile ranges.

**Figure 2.** Distribution of Wilcoxon scores between doses of diazepam cream for anal pain and anal bleeding using the Wilcoxon rank-sum test. Diamonds represent Wilcoxon mean scores.
positive response to bleeding, and 11 (68.8%) demonstrated a complete response. Sixteen (94.1%) patients who received the 4% dose also experienced a positive response and 11 (64.7%) developed a complete response. The median days for improving bleeding were 7 days for all cohorts.

All patients reported using diazepam cream daily until symptoms subsided or were still using it at time of follow-up. Twelve (32.4%) overall patients, 8 from the 2% (42.1%), and 4 (22.2%) from the 4% group were actively using diazepam cream at follow-up (Table 4). However, there was no statistical difference with continued cream use among the groups. Eight of 13 patients (61.5%) who demonstrated a complete pain response had discontinued diazepam cream at follow-up; 5 of the 8 were using the 2% dose. Thirteen of 22 (59.1%) patients who experienced a complete bleeding response were not using diazepam cream at follow-up; of these, 3 were using the 2% dose. The median duration of follow-up for patients not using diazepam cream with complete anal pain and bleeding response was 8.8 and 7.6 months, respectively.

As reported in Table 4, the median patient satisfaction score (0–5) was 4.0 for the entire cohort and the 2% group and 4.3 for the 4% group. Three patients, 2 from the 2% cohort and 1 from the 4%, did not have adequate symptoms relief and required alternative treatments. One patient switched to nifedipine cream, and 2 required lateral sphincterotomy as definitive therapy. Only 1 patient in the entire study experienced an adverse effect, which was perianal pruritus from using the 4% dose.

Twenty (54.1%) patients used traditional treatments as monotherapy or combination therapy prior to diazepam cream use. The treatments included nifedipine cream (1 instance), nitroglycerin cream (1), Reticare cream (1), dibucaine cream (1), preparation H cream (2), hydrocortisone cream (2), nonsteroidal anti-inflammatory drugs (8), and conservative treatments such as sitz baths, high fiber diet, and stool softeners (8).

Patients who reported prior traditional anal fissure therapies stopped those therapies before starting diazepam cream, as the traditional therapies provided inadequate symptomatic relief. Thus, all patients were considered to be, at the start of the study, free of any systemic effects of alternative anal fissure treatments.

4. Discussion

The current first line of treatment for symptomatic anal fissure is topical nitroglycerin[7] and/or calcium channel blockers such as nifedipine[8] and diltiazem.[9] Historically, surgical approaches such as lateral sphincterotomy have been a common method to relieve anal pain secondary to chronic anal fissures in those who do not respond to these topical therapy. However, patients are hesitant due to high cost and risk of fecal incontinence.[18] As a muscle relaxant, topical diazepam could theoretically treat the symptoms of chronic anal fissures. No prior literature on topical diazepam as potential treatment for anal fissures or anal pain has been found after searching ClinicalTrials.gov, PubMed, Cochrane Library, Scopus, CAM-QUEST, CAMbase, and IndMed.

In our patient population, the effects of diazepam cream on chronic anal fissure symptomatology were promising. Both 2% and 4% groups noticed a significant reduction in pain and bleeding following therapy. Only 1 patient in each group reported no response to bleeding. Interestingly, the median NRS score fell more progressively from 8.0 to 2.0 with the 2% cream as compared with 8.0 to 2.0 with the 4% dose (Table 3). Similarly, median bleeding reduction was greater in the 2% cohort, from 7.0 to 2.0, when compared to the 4% group’s reduction from 6.0 to 2.0. Pain persisted in 2 (11.8%) patients treated with 4% dose, whereas all the 2% cohort had complete resolution. Although the results appeared to be greater for the 2% dose, ultimately there were no statistically significant differences between the groups, suggesting possibly that the 2% dose provided maximum symptomatic therapeutic effects. A greater percentage of patients in the 2% group were using the cream at follow-up when compared to the 4% cohort (42.1% vs 22.2%), and this could be another explanation for why the lower dosage cohort experienced greater symptomatic relief.

Conventional myorelaxant creams such as topical nitroglycerin, nifedipine, and calcium channel blockers have all proven to be efficacious in treating anal fissures, albeit less so than lateral internal sphincterotomy. Unfortunately, different studies have reported associated moderate to severe side effects, ultimately resulting in poor compliance and treatment failure.[20] Nitroglycerin causes headaches and hypotension in over 70%
of patients[7,22] and diltiazem causes perianal itching.[9] Compared to nitroglycerin, nifedipine and diltiazem are less efficacious but have reduced incidence of side effects.[10] Nevertheless, patients prefer topical therapy, as the reported adverse effects are more desirable than the potential risk of postsurgical complications, such as incontinence.

In comparison, diazepam cream adverse effects were minimal in this study; only 1 patient (4% cohort) reported perianal itching. External anal sphincter relaxation carries the risk of fecal incontinence, but no patient reported such events. No patients reported systemic side effects, including those that took medications with potential interactions with diazepam. As such, we did not need to compare side effect profiles of concurrent medications between patients. However, further studies with serum measurement of diazepam and its metabolites are required to assess pharmacokinetics of anal administration. Patient satisfaction, supported by the near absence of side effects, was nearly identical and positive in both groups.

Our choice of using symptoms relief as the primary outcome is supported by prior studies, including 1 on nitroglycerin cream for chronic anal fissure treatment,[16] which led to its Food and Drug Approval process for treatment of symptomatic anal fissures. Limitations of our study include its open-labeled nature, retrospective design, and non-randomized treatment groups. Thus, the results of this pilot and proof of concept study need to be validated and confirmed by future randomized, double-blind trials. The lack of a control group was also a limitation for this study. Again, this study’s purpose was to determine if diazepam cream can successfully relieve the symptoms of anal fissures. Because there were no statistically significant differences between the NRS scores and ABS of the 2 doses, we did not pursue a dose-response study. In addition, anorectal manometry was not completed at follow-up, which would have provided objective data for a dose–response curve. Future studies using anorectal manometry can also assist in confirming the greater efficacy of diazepam cream when compared to placebo by demonstrating lower sphincter pressures. Furthermore, anorectal manometry might possibly assist in delineating a precise mechanism of action; a potential mechanism is external sphincter relaxation resulting in reduction of ischemia and pain relief. Another limitation is that we did not assess healing of fissures at the conclusion of treatment. Thus, it could not be determined if diazepam cream only resolved symptoms or if it also led to fissure healing. We can only assume that chronic anal fissures must have been healed in over 65% (Table 4) of patients, those that had already discontinued therapy at follow-up. Persistence of pain relief after therapy discontinuation strongly suggests healing. Nevertheless, objective measure of anal fissure healing should be included in a future randomized, double-blind study.

Treatment of chronic anal fissures remains a challenge even today. In our study, topical diazepam proved to be an effective and well tolerated treatment of chronic anal fissure symptoms. Although it is unclear whether the effects of diazepam cream are sustainable, these results could provide clinicians another treatment option. Randomized, double-blind, placebo-controlled and long-term outcome trials should be conducted to enhance and validate the findings from this study.

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