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PERIANAL APPLICATION OF GLYCERYL TRINITRATE OINTMENT VS TOCOPHERAL ACETATE OINTMENT IN THE TREATMENT OF CHRONIC ANAL FISSURE: A RANDOMIZED CLINICAL TRIAL

Running title: Tocopherol acetate vs glyceryl trinitrate for anal fissure

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ABSTRACT:

Background: Medical treatment, including glyceryl trinitrate ointment represents the first step for the management of chronic anal fissure. However, glyceryl trinitrate ointment is associated with headache and consequently, a high withdrawal rate of the treatment

Objective: The aim of the present study was to evaluate the effect of the topical application of tocopherol acetate ointment on pain relief and chronic anal fissure epithelialization, comparing it with the effect of a standard treatment with glyceryl trinitrate ointment.

Design: Two parallel-group, single center, randomized, controlled intent-to-treat clinical trial.

Settings: Garcilaso Clinic affiliated with Universidad Alfonso X (Madrid, Spain)

Patients: Patients with chronic anal fissure.

Interventions: Patients were randomized into 2 groups: patients receiving tocopherol acetate ointment and patients receiving glyceryl trinitrate ointment.

Main outcome measures: The primary end-point was quantification of anal pain 8 weeks after beginning the treatment as measured by Visual Analogue Scale ranging from 0 to 100 mm. The secondary end-points were the healing rate (during the treatment period of 8 weeks) and the recurrence rate.

Results: Hundred sixty consecutive patients were treated, 80 in each group.

By eight weeks after treatment, mean anal pain score declined by 56.2 mm in the glyceryl trinitrate ointment group compared to a mean anal pain score decline of 67.1 mm in the tocopherol acetate ointment group (mean difference: 10.9 mm (95% confidence interval; 4.3 to 18.6; p=0.018).

Sixteen weeks after finishing the therapy recurrence rate was 13.2% in the glyceryl trinitrate ointment group vs 2.9 in the tocopherol acetate ointment group (p=0.031).

Limitations: Absence of manometric measurements of the internal anal sphincter before and after the treatments. glyceryl trinitrate ointment as active comparator, whereas calcium-channel blockers are actually the gold-standard treatment.

Conclusions: Anal pain was significantly lower in the tocopherol acetate ointment group than in glyceryl trinitrate ointment group at 8 weeks after treatment. tocopherol acetate ointment achieved a greater healing rate and a lower recurrence rate 16 weeks after finishing the treatment.

ClinicalTrial.gov Identifier: NCT03787030.

Key words:

Tocoperol acetate ointment; Glyceryl trinitrate ointment; Anal fissure

INTRODUCTION

Chronic anal fissure is one of the most common benign anorectal conditions. Constipation is considered a triggering factor in many cases, causing a trauma to the anoderm with the passage of a hard stool. The persistence of the fissure is typically associated with anal sphincter hypertonia. Thus, the treatment of chronic anal fissure aims to reduce the sphincter high pressure, allowing adequate blood flow to the fissure and consequently promoting the healing of the fissure[1.].

Medical treatment represents the first step for the management of chronic anal fissure. Surgical therapy is reserved for refractory anal fissure. Although medical therapy is less effective than surgery, it should be offered first because of its better tolerance, and lack of severe complications (ie, fecal incontinence)[1.-3.].

Aside from supportive measures (fiber, sitz bath, stool softener), patients with chronic anal fissure are usually prescribed topical vasodilators (nifedipine, diltiazem or nitrates). Vasodilators promote the healing of anal fissure by increasing local blood flow and reducing pressure in the internal anal sphincter. The observation that the posterior commissure of the internal sphincter is less perfused than the other sections led to the concept that ischemia could be contributing to the persistence of anal fissure. Despite short term efficacy of medical conservative treatment, up to 50% of patients successfully treated developed recurrent fissure[1.,4.].

The intense anal pain is attributed to the increased pressure of the internal anal sphincter. Thus, systemic analgesic drugs or local anesthetics are often used as coadjuvant treatments. The pain is associated with the anodermal tear, which causes a local inflammatory response, with release of cytokines that irritate nociceptive receptors[1.]. Consequently, we hypothesize that the use of immunomodulating agents may reduce the

postoperative pain, decrease the sphincter spasm and consequently improve the fissure healing[5].

The aim of the present study was to evaluate the effect of the topical application of tocopherol acetate on pain relief and chronic anal fissure epithelialization; and to compare it with the effect of a standard treatment with topical glyceryl trinitrate.

PATIENTS AND METHODS

A prospective, randomized clinical trial was performed. Inclusion criteria were patients with a diagnosis of chronic anal fissure treated at our institution between December 2018 and February 2019, and accepting to participate in the study and signing a written informed consent form. Exclusion criteria were patients recurrent fissure, intestinal inflammation disorders, immunosuppression, HIV, tuberculosis, or sexually transmitted diseases. Pregnant or lactating women, patients under 18 years of age and subjects with a history of headaches, heart disease, intolerance to nitrates and closed angle glaucoma (specific contriandications for glyceryl trinitrate ointment) were also excluded. Patients with either posterior or anterior based fissures were included.

Chronic anal fissure was defined as a persistent anal fissure despite hygienic and dietary measures (warm sitz bath, high-fiber diet, fiber supplements, high intake of liquids and also ad libitum over-the-counter analgesics) over a ≥ 6-week period. Any patient with symptoms longer than 6 weeks and the presence of anal fissure was included. Hygienic and dietary measures for 6 weeks were prescribed and controlled by the General Practioners. Patients presenting with 6 weeks of symptoms, but without having followed hygienic and dietary measures previously, assessed by self-report, were not allowed to

participate. Following our protocol, ointments are only prescribed after the evaluation by a coloproctologist.

Sample size calculations used was based on personal experience of anal pain (non-published data) related to chronic anal fissure after the treatment with Glyceryl trinitrate ointment (GTO) of 20 $\pm$ 4 mm, and an expected reduction of pain after tocopherol acetate ointment (TAO) to 10 mm, 8 weeks after beginning the treatment. To achieve 80% power at a significance level of $p < 0.05$ on a two-sided two-sample equal-variance t-test, 80 patients were required for each arm of the study. Patients were randomly assigned using a pseudo-random-number generator with randomly permutated blocks, intentionally to achieve a 1:1 ratio of males between groups and a 1:1 ratio of females between groups. Subjects were assigned to Tocopherol acetate ointment (TAO) (experimental group) and GTO (control group) groups at a 1:1 ratio (Table 1).

Interventions

Glyceryl Trinitrate Ointment (GTO)

Commercially available aluminium tubes containing 0.4% GTO (Rectogesic, ProStrakan Group, Galashiels, United Kingdom) were purchased from pharmacies. Patients were instructed to use a small amount (2.5 ml), estimated at about 375 mg of ointment (containing 1.5 mg of glyceryl trinitrate), applied with a gloved finger to the distal anal canal, every 12 hours for 8 weeks.

Tocopherol Acetate Ointment (TAO)

Commercially available plastic tubes containing 100% TAO (Filme Olio, Hulka SRL, Rovigo, Italy) were purchased from pharmacies. Patients were instructed to use a small

amount, estimated at about 1 ml of ointment, applied with a gloved finger to the distal anal canal, every 12 hours for 8 weeks.

Additional conservative measures in both groups included a high fiber diet with avoidance of constipation and a daily sitz bath. These recommendations should be maintained during at least 6 months after having finished the treatment.

Definitions

Healing of the chronic anal fissure was defined as the absence of symptoms (rectal bleeding, and anal pain) and complete epithelialization of the fissure, as determined by physical examination. Epithelialization was defined as the complete cover of the fissure by skin or mucosal tissue. Recurrence was defined as the appearance of new symptoms and evidence of an anal fissure on physical examination, after having finished the prescribed treatment.

Variables

The variables recorded at baseline were the presence of rectal bleeding and anal pain during the defecation. Anal pain was assessed as a subjective perception rated on a visual analog scale (VAS), with 0 mm indicating complete absence of pain and 100 mm indicating unbearable pain.

Follow-up visits were made 2, 8, and 24 weeks after the beginning of the treatment. The number of patients lost to follow-up or discontinuing the treatment, because of any reason were also recorded. The patients were informed that the follow-up is essential to evaluate the correct healing and prevent from future recurrences. One of us (Carolina Llavero)

called each patient who missed or rescheduled an appointment, with the goal of 100% follow-up.

Compliance with GTO and TAO treatments was assessed based on patient self-reports.

The primary end-point was quantification of anal pain, as measured by VAS, 2 and 8 weeks after beginning the treatment. The secondary end-points were the healing rate (during the treatment period of 8 weeks) and the recurrence rate for both treatments 24 weeks after beginning the treatment and 16 weeks after having finished it. All of the outcome measures (pain perception, as measured by VAS, re-epithelialization, and recurrence) were assessed by the same coloproctology nurse blinded to the treatment.

Statistical Analysis

Data were collected by an independent data manager and analyzed by an independent statistician. An independent data monitoring committee supervised the compliance with the study protocol and the correct collection of the data.

Quantitative variables were defined as the mean and SD or as the median and range for nongaussian variables. Qualitative variables were reported as frequencies and percentages.

The χ^2 test was used for comparison of qualitative samples. Statistical significance was set at a level of $p < 0.05$. Wilcoxon test was used to assess whether improvement from baseline in VAS anal pain score was different by treatment group. An intention-to-treat analysis was performed; there were no missing data from the patients withdrawn from the treatment assigned.

The study was approved by the Institutional Review Board (protocol No. Garcia 2018-12) and meets the guidelines of the responsible governmental agency. All of the patients

signed an informed consent form to participate in the study. The study is registered in the ClinicalTrial.gov database with the number NCT03787030.

RESULTS

Hundred sixty consecutive patients were treated between December 2018 and February 2019. There were 90 women (56.2%) and 70 men (43.8%), with a mean age of 49.6 ± 8.2 years. 148 patients presented with a posterior fissure and 12 with an anterior one (7 patients assigned to GTO group and 5 to TAO). Anal pain was present in 160 patients (100%), and rectal bleeding, which occurred in 113 patients (70.6%). There were no significant differences in clinical symptoms between groups (Table 2).

Compliance with the treatment and complications

Among the patients treated with GTO, 22 (27.5%) reported mild-to-moderate headache, but 14 patients (17.5%) reported severe incapacitating headache and led to their withdrawal from treatment during the first 2 weeks of therapy. Among the patients under TAO treatment, there were no adverse effects reported. Thus, the withdrawal rate was significantly higher in the GTO group ($p < 0.001$). All the patients of both groups, excepting those ones who abandoned of GTO group referring headache, reported full compliance with the prescribed treatment. In the 14 patients withdrawn from treatment surgery was indicated (lateral internal sphincterotomy).

Pain relief

Following an intention-to-treat analysis, after 2 weeks of treatment, 49 patients (61.2%) in the GTO group were asymptomatic, whereas 59 patients (73.8%) were asymptomatic in the TAO group ($p = 0.09$). Mean anal pain, as measured by VAS, was 43.2 $\pm$ 8.3 mm

(range, 0 – 90 mm) in the GTO group and 24.8 ± 4.6 mm (range, 0 – 70 mm) in the TAO group (p = 0.008). By two weeks after treatment, mean anal pain score declined by 35.6 mm in the GTO group compared to a mean anal pain score decline of 52.1 mm in the TAO group (mean difference: 16.5 mm (95% confidence interval; 7.2 to 28.4; p = 0.002). After 8 weeks of treatment (end of treatment), 56 patients (70%) in the GTO group were asymptomatic, whereas 70 patients (87.5%) in the TAO group (p = 0.007). Mean anal pain, as measured by VAS, was 22.6 ± 4.4 mm (range, 0 – 60 mm) in the GTO group and 9.8 ± 1.4 mm (range, 0 – 35 mm) in the TAO group (p = 0.002). By eight weeks after treatment, mean anal pain score declined by 56.2 mm in the GTO group compared to a mean anal pain score decline of 67.1 mm in the TAO group (mean difference: 10.9 mm (95% confidence interval; 4.3 to 18.6; p = 0.018).

Excluding the patients who discontinued the treatment in the GTO group, we failed to demonstrate significant differences in the percentage of asymptomatic patients between groups (73.8% in TAO vs 74.2% in GTO (p = 0.946) at 2 weeks after treatment, and 87.5 in TAO vs 84.8% in GTO (p = 0.643) at 8 weeks after treatment). However, at both time points, anal pain was significantly lower in TAO group (24.8 mm (range 0 - 70) in TAO vs 43.2 mm (range (0-90) in GTO (p=0.008) at 2 weeks after treatment, and 9.8 mm (range 0 - 35) in TAO vs 22.6 mm (range 0 - 60) in GTO (p = 0.002).

Healing

Two weeks after the beginning of the treatment, complete epithelialization of the fissure was observed in 15 patients (18.7%) in the GTO group and 20 (25%) patients in the TAO group (p = 0.07). Of the 14 patients who discontinued GTO treatment, only 2 reported partial relief, but the rest did not notice any improvement, as they discontinued the treatment before the 3rd day after beginning with it.

After 8 weeks of treatment (end of treatment), complete epithelialization was observed in 86.3% of patients in the TAO group and 66.3% of patients in the GTO group (observed difference 20%, 95% confidence interval 5.9% to 33.2%, p = 0.003). Based on the definition of healing (absence of symptoms associated with complete re-epithelialization), healing was achieved in 53 patients (66.3%) in the GTO group and 69 patients (86.3%) in the TAO group (p = 0.003).

Excluding the patients who discontinued the treatment in the GTO group, we failed to demonstrate significant differences in complete epithelialization rate between groups (25% in TAO vs 22.7% in GTO (p = 0.749) at 2 weeks after treatment, and 86.3% in TAO vs 80.3% in GTO (p=0.335) at 8 weeks after treatment).

Recurrence

Sixteen weeks after finishing the therapy (24 weeks after beginning treatment), anal fissure had recurred in 8 of the 53 healed patients in the GTO group (13.2%) and in 2 of the 69 healed patients in the TAO group (2.9%) (p = 0.031). Main outcomes following an intention-to treat analysis are shown in Table 3.

All of the patients who showed no clinical improvement, those who abandoned treatment, and those who presented with recurrence underwent surgical lateral internal sphincterotomy. Complete resolution of the fissure was achieved in all the patients undergoing lateral internal sphincterotomy.

DISCUSSION:

In the present study we have observed that TAO obtained a greater pain relief and greater healing rate than GTO, when following an intention-to-treat analysis, as TAO was not associated with adverse effects. However, the small sample size probably prevented from obtaining significant differences when excluding the patients withdrawn from GTO treatment. Among patients with initial healing, recurrence rate was also lower in the TAO group.

The initial treatment of anal fissure is with medical interventions. Topical nifedipine and diltiazem work by reducing anal sphincter tone, which promotes blood flow and faster healing. Topical nitroglycerin acts as a vasodilator to encourage increased blood flow to the area of the fissure, increasing the rate of healing[6.]. A third pharmacological method is botulinum toxin, which is more effective than nitrates and calcium channel blockers, but the local injection is painful, and it has also temporary effect[7.]. A recent study of our group showed that percutaneous posterior tibial nerve electrical stimulation could also be considered a safe and effective alternative treatment for anal fissure, being in some ways superior to topical nitroglycerin[8.].

The healing rate of anal fissure under topical nitroglycerin treatment varies from 60% to 80%. However, the main drawback to this therapy is headache, which leads in up to 20% of patients to withdrawal from treatment, which must be subtracted from the percentage of healing rate in an intention-to-treat analysis. In addition, recurrence rates between 30-50% have been reported[9.-12.]. Despite the aforementioned adverse effects of nitroglycerin, in our country GTO is actually considered the topical treatment of choice, as tubes containing GTO are commercially available, whereas nifedipine or diltiazem ointments or gels must be elaborated at a compounding pharmacy, and consequently more difficult to be accessed nowadays. In our previous study on anal fissure, patients under GTO

treatment achieved a complete healing, defined by complete epithelialization and absence of symptoms, in 65% of the cases, but with a 11.5% of recurrence rate 16 weeks after having finished the treatment[8.]. Similar results have been observed in the GTO group of the present study, with 66.3% of healing rate and 13.2% of recurrences[8.].

Vitamin E is an essential micronutrient with strong antioxidant activity. Alpha-tocopherol is the isoform favoured by the human cells. Tocopherol acetate has been involved in immune functions, cell signaling, regulation of gene expression and other metabolic processes. In addition, it also increases the expression of two enzymes that supress arachidonic acid metabolism, thereby increasing the release of prostacyclin from the endothelium, which induces vasodilation[13.]. As anal fissure is considered an ischemic lesion, the improvement of local blood supply to the tearing mucosa, allows the healing of the fissure, in a similar mechanism to GTO. Specially in burn lesions, it has been shown that topical tocopherol acetate stimulates the formation of granulation tissue, modulates angiogenesis and improves epithelialization and wound healing[14.-16.].

Its topical application has also shown an anti-inflammatory effect in diverse dermatological diseases, reducing the edema and modulating the increase of cyclo-oxygenase- 2 (COX-2), the enzyme that catalyzes the synthesis of prostaglandin E2, participating in the local inflammatory response[17.]. Thereby, the anti-inflammatory effect, reducing the local inflammatory response against the tissue damage, has been proposed as the basis of a topical analgesic effect[18.,19.]. The modulation of the inflammatory response may reduce cytokines release irritating nociceptive receptors[19.-21.]. The intense pain associated with the fissure, and exacerbated during the deposition of hard stools, provokes a spasm of the internal anal sphincter, and impairs the necessary blood supply for fissure healing. The eventual analgesic effect of tocopherol acetate may also contribute to reduce the sphincter hypertonia and improve local vascularization. These

effects may not only act in the short-term healing, but also last for a longer period, preventing from the recurrence of the fissure. In addition to the absence of adverse effects, the main benefits of TAO are the reduction of anal pain and the lower recurrence rate. Both entities are probably related with the immunomodulator effect of vitamin E on acute and chronic inflammatory response.

Limitations:

The main limitation of the present study is the use of GTO as active comparator with TAO therapy. Calcium channel blockers are actually considered the gold standard treatment for chronic anal fissure, with similar or even greater healing rates and without the adverse effects of GTO. However, we decided to use GTO as active comparator, because the latter are usually specially compounded medications in our country, more difficult to be obtained by the patients and with a potentially higher variability in their compositions. Future studies should be conducted comparing TAO with topical calcium channel blockers.

In addition, the GTO frequency of administration every 12 hours may not be sufficient and often this medication is prescribed three times a day, at least due to half life of medication. Probably, if patients would have used it more often the success rate might have been different.

It is expected that TAO decreases the sphincter tone due to the antinflammatory properties. However, in the present study we did not obtain any objective measurements of anal pressure. It would be interested to conduct future studies, evaluating the changes in manometric pressures of the internal anal sphincter after TAO treatment.

Furthermore, the design of this study is an intention-to-treat protocol. Thereby, the greater healing rates in the TAO group were mostly based on the high withdrawal rate in GTO

group. Further investigations must include greater sample sizes to elucidate superiority or non-inferiority of TAO treatment, when compared with GTO or calcium channel blockers.

Despite outcome measures were assessed by a coloproctology nurse blinded to the treatment, the patients were not blinded to the treatment prescribed. Future studies should consider blinding the patient to the treatment assigned.

Finally, we established pain relief as main outcome of the study and made healing as secondary outcome. In our opinion, pain is the most relevant symptom for the patient and pain relief appears before complete achieving complete healing.

CONCLUSION:

Anal pain was significantly lower in the TAO group than in GTO group at 2 and 8 weeks after treatment. TAO achieved a greater healing rate and was not associated with adverse effects. Recurrence rate was also significantly lower in the TAO group 16 weeks after finishing the treatment. Accordingly, TAO can be considered a safe and effective alternative to GTO for the treatment of anal fissure. Future studies should confirm these results.

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Disclosure of interest:

The authors report no conflicts of interest.

Authors´contributions:

- Data acquisition: Ruiz-Tovar, Llavero

- Drafting of manuscript: Ruiz-Tovar
- Critical revision of manuscript: Llavero

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