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ORIGINAL ARTICLE

Efficacy of the Use of Topical Tadalafil in The Treatment of Anal Fissure. Results of a Cooperative Study

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ABSTRACT
Introduction: *The medical treatment of chronic anal fissure has multiple options. Tadalafil was hardly analyzed in the literature as a therapeutic option.*
Objective: *To evaluate the safety and effectiveness of the use of topical Tadalafil for the medical treatment of anal fissure.*
Design: *Observational non-randomized prospective study.*
Patients and methods: *Patients with chronic anal fissure lasting more than 8 weeks treated with Tadalafil during the 2011-2018 period were analyzed. Those who did not complete treatment were excluded. Cure rate, adverse effects, treatment time and its relationship with response were recorded.*
Setting: *Two private medical institutions.*
Results: *Eighty-six patients, 53 men (61%), 77 of them older than 55 years, were analized. Cure was achieved by 82.5% of patients, 11.6% underwent surgery, and the remaining patients continue chronic medical treatment with a good clinical response. Seventy-two percent of patients had 2 months of treatment (p = 0.002); 7 patients, 3 months; 12, between 3 and 6 months; and 5, more than 6 months. Sixty-four percent of patients did not present previous anal pathology and the rest did not modify their results despite the association. No adverse was presented in 95% of patients and those reported (rush, thrombosis, light bleeding) were mild.*
Conclusion: *Treatment with Tadalafil has a high cure rate and symptomatic resolution with almost no side effects. In failure cases surgery resolved the condition. The performance of other comparative studies with other pharmacological methods and/ or surgical treatment could affirm these results.*

Keywords: *Anal fissure; Tadalafil; Sphincterotomy; Nitrites*

INTRODUCTION

Anal fissure is one of the most frequent condition in the proctological consultation and despite the fact that there is sufficient evidence and numerous therapeutic possibilities, treatment is still challenging, in some cases controversial and refractory in a considerable number of patients.[1,2]

Anal fissure is a painful lesion that presents as an ulceration, usually located in the posterior anal canal. It is acute when does not extend beyond 6 to 8 weeks. After this period, it is considered chronic, associated with the persistence of symptoms and physical findings of hypertrophic papilla, sentinel hemorrhoids, and visualization of the internal anal sphincter (fissure syndrome).[3,4]

Given the possible disability associated with surgery, the immediate future with the consequent risk of continence disturbances, new medical treatment alternatives are being considered.[2-5] The use of Tadalafil, a potent selective phosphodiesterase inhibitor, is recent and has not been sufficiently studied as a therapeutic option to heal anal fissures. There is no national history with this treatment.

It has been shown in vitro that phosphodiesterase 5 is responsible for the degradation of cyclic GMP within the smooth muscle cell, and its inhibition by Tadalafil translates into the persistence of high levels of cyclic GMP with the consequent relaxation of the anal sphincter. Additionally, in an optimal state of functioning, the smooth muscle cell is capable of synthesizing type III collagen, proteoglycans and elastin that promote healing.[6]

The objective of this study was to assess the safety and effectiveness of the use of topical Tadalafil for the treatment of anal fissure.

MATERIAL AND METHODS

All patients who spontaneously attended the outpatient clinic of two private medical institutions (one university) between July 2011 and July 2019 and had anal fissure evident on physical examination, and symptoms duration ≥ 8 weeks were prospectively registered.

Patients with previous medical or surgical treatment or associated anal pathologies were not considered as exclusion criteria. Patients who could not or did not complete treatment for reasons not related to treatment were excluded.

Patients who met the selection criteria were consecutively included in a spreadsheet database (Microsoft Excel®) registering age, gender, previous surgery, length of treatment, treatment results, adverse effects of the drug and associated complications.

The definition of variables was as follows:

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- Treatment outcome with Tadalafil was defined as:
  - Healing: definitive cure with medical treatment.
  - Chronification: need to continue medical treatment due to persistence of disease.
- Need for surgery due to lack of response.
- Time of treatment was defined as the length of time from the beginning to the end of treatment with Tadalafil:
  - 1 month.
  - 2 months.
  - 3 months.
  - > 3 months.
- Previous anal pathology was defined as:
  - None: no medical history.
  - Hemorrhoids, fistula, etc.
  - Previous surgery for anal fissure

All patients were clinically evaluated before treatment and during follow-up monthly for 6 months and then annually.

Setting

Coloproctology Service of Sanatorio Modelo de Tucumán, , and the Centro Médico Alberti, Buenos Aires, Argentina.

Formula

Tadalafil topical cream, applied 3 times a day, was prepared masterfully at both medical centers based on the formula proposed by Alfonzo Nuñez et al.,[6] and consisted of:

- Polyester mucopolysaccharide of sulfuric acid (heparinoid organ) 4 mg.
- Prednisolone 1 mg.
- Oxypolyethoxydodecane 50 mg.
- Hexachloraphene 5 mg.
- 2% lidocaine hydrochloride.
- Tadalafil 40 mg.

RESULTS

A total of 86 patients, 53 (61%) men, diagnosed with anal fissure were studied (Fig. 1).

According to age,77 were over 55 years. No significant difference could be shown between the three age groups evaluated (Fig. 2).

Results of treatment withTadalafil, detailed in Fig 3, show that 71 (82.5%) patients achieved cure, while 10 (11.6%) had to undergo surgery due to failure. The remaining 5 (5.8%) patients continue chronic medical treatment, although with a final good response and disappearance of symptoms. These patients were assessed separately from the ones cured, although they were able to spare surgical treatment. If all cases with a favorable response to symptoms withTadalafil were included, a cure rate of 88% should be considered (Fig. 3).

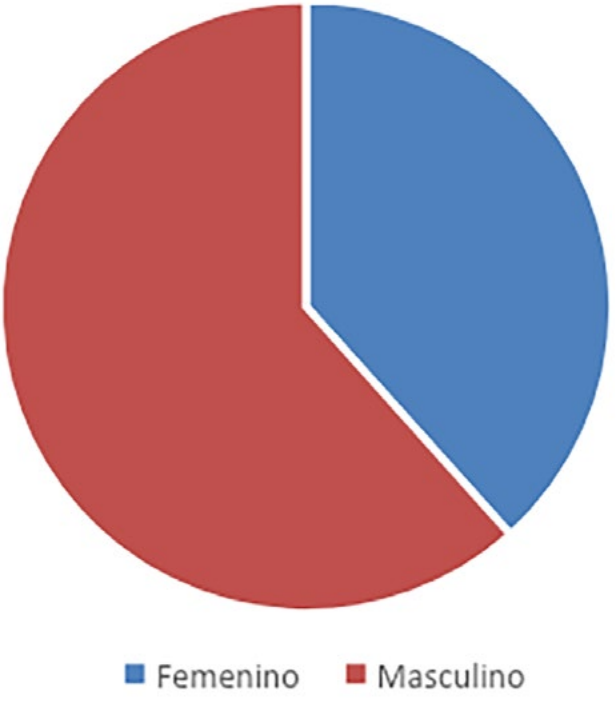

Figure 1: Gender distribution.

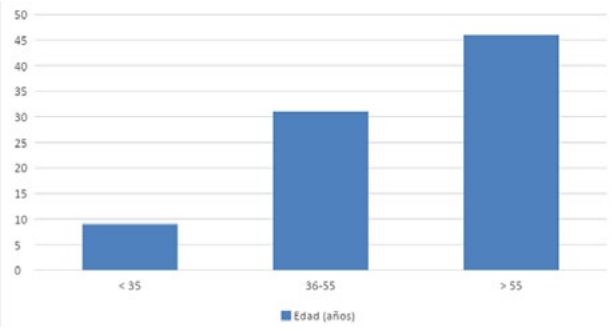

Figure 2: Age distribution.

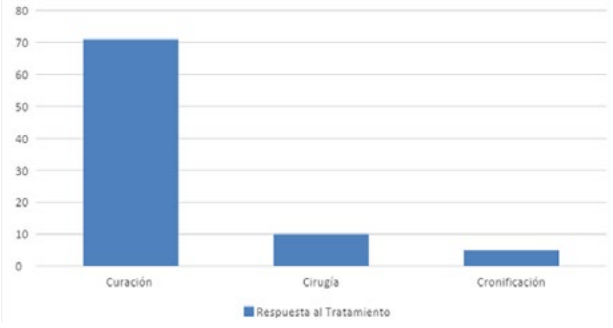

Figure 3: Treatment results.

Regarding the length of Tadalafil treatment, it was observed that 62 (72%) patients applied the cream at least for 2 months 7(8%) for 3 months, 12 (14%) between 3 and 6 months and 5 (6%) for more than 6 months (p = 0.002) (Fig. 4).

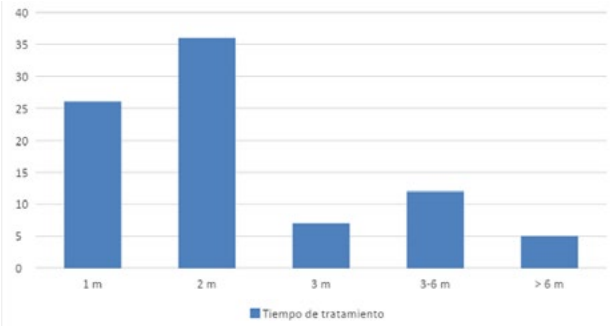

Figure 4: Length of treatment with Tadalafil.

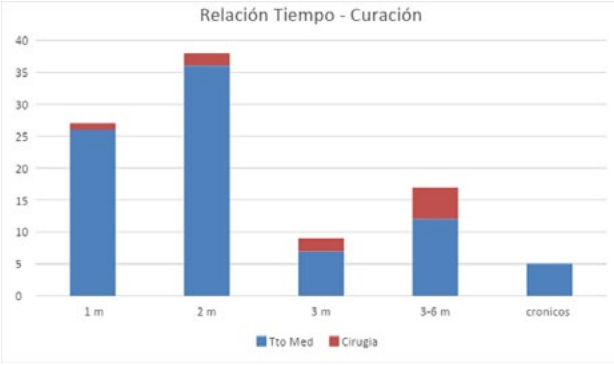

Figure 5: Relationship between treatment time and Medical treatment - surgery

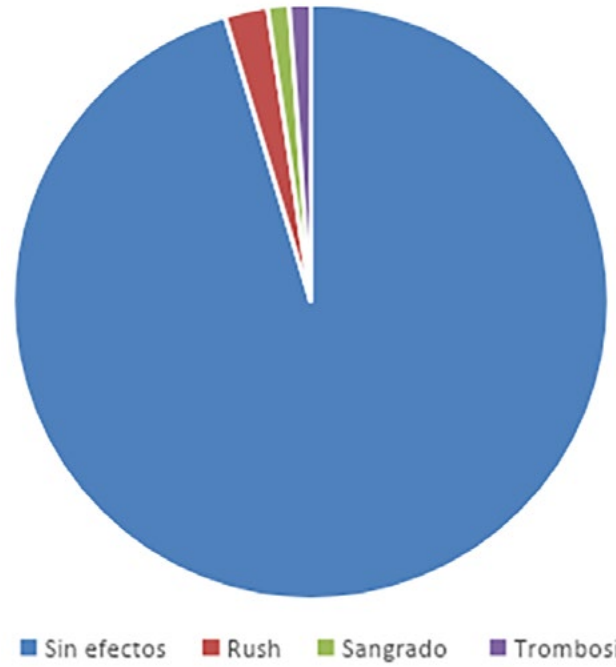

Figure 6: Adverse effects of treatment with Tadalafil .

When analyzing the relationship between treatment time and its outcome, it was observed that 83% of patients that achieve cure required 2 months of treatment (n=59) and 3 of that group required surgery. On the other hand, 2/7 patients treated for 3 months and 5/12 patients treated during 3 to 6 months were operated on, overall 11% underwent surgical treatment (p = 0.54) and 6% needed chronic medical treatment (Fig. 5).

With regard to the variable prior anal pathology, 64% of patients had none, while hemorrhoidal disease was the most prevalent (17%), without statistical significance.

Regarding the adverse effects variable, it was observed that 82 (95%) patients did not present any, while 2 had a skin rush that subsided with the progressive suspension of treatment, 1 had an external thrombosis and 1 had mild bleeding that resolved spontaneously. No case of headache, pressure sensation or heaviness similar to that produced by the use of oral vasodilators was recorded. Likewise, there were no central or peripheral cardiovascular effects, or continence alterations of any kind (Fig. 6).Follow-up was monthly for the first 6 months and then annually up to 2 years. This follow-up (2 years) could be achieved in 91% of cases, and no early recurrence was recorded after healing was achieved. Two patients recurred after 2 years and required surgery.

DISCUSSION

The treatment of anal fissure is based on hygienic-dietetary measures and pharmacological methods that relax the smooth muscle such as ointments based on nitric oxide (neurotransmitter that prevents muscle contraction), calcium channel blockers (nifedipine and diltiazem), or the application of botulinum toxin.[1,2,7-10]

Some of these drugs (nitroglycerin and calcium blockers) are associated with various adverse effects such as headache, lipothymia, dizziness and hypotension, leading to discontinuation of treatment.[3-5]

With regard to botulinum toxin, a clear association among dose, preparation, injection site, and cure rates was found, apart from to the high cost of treatment and the possibility of recurrence ≥60% after stopping treatment.[11]

Sphincterotomy is more effective than botulinum toxin at 3 years, despite an incontinence rate of 9%.[11] For lateral sphincterotomy 92-100% of healing and 3.3-16% of incontinence have been informed.[7,10]

In a Cochrane review, medical treatment with nitrites, calcium blockers ,or botulinum toxin have better results than placebo, although is less effective than surgery. Nitrites heal up to 49% of patients with a 50-60% recurrence. The efficiency of botulinum toxin is 67.5%.[2]

Nifedipine is superior to nitrites with fewer side effects and drug interactions.[7,8]

Medical treatment has fewer consequences than surgery (recommendation 1B); for this reason and its safety represents the first-line treatment (recommendation 1B).[5] Calcium channel blockers have fewer side effects and constitute the first line (recommendation 1A).[5] Botulinum

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toxin is similar to medical treatment with better healing and constitutes the second line treatment (recommendation 1 C).[5,8-10]

The side effects of nitrites (headache), the transient incontinence secondary to botulinum toxin informed in some reports and the definitive incontinence associated with surgery, despite its high effectiveness make it necessary considering other treatments.

There is almost no bibliography regarding the use of topical Tadalafil in the treatment of anal fissure. Currently it is not commercially available for topical application, so we made a magisterial formula according to that proposed by Alfonzo Nuñez, et al.,[6] whose results we were able to reproduce. Although in the international pharmaceutical market Tadalafil exists as an oral product or topical jelly, we could not found evidence of its use for the topical treatment of anal fissure, except for the aforementioned study.

Our series showed that 83% of patients who used Tadalafil during an average time of 2 months achieved cure. If we consider those that improved their clinical picture but for multiple reasons continued their treatment chronically, the rate reached almost 88%, constituting in these cases an option for patients with a contraindication to surgery.

In correlation to Alfonzo Nuñez, et al. study,[6] published in 2012, we demonstrated a high rate of satisfactory response with the use of Tadalafil. It was demonstrated in this study that 10% of patients required surgery for resolution, an index slightly higher than the series reported by each of the participating centers in this study separately.

Unfortunately, there are no comparative studies of Tadalafil with lateral sphincterotomy or with other medical treatments. In this series, the non-comparative design is based on the high rate of side effects observed with other drugs (nitrites) and the low response rate associated with these and common creams. In the same way, surgery is only indicated after the failure of medical therapy.

In the analysis of the duration of treatment and its relationship with results, no significant evidence was found, so a new line of research indicates the need of a larger sample of patients to be treated with Tadalafil, since our experience reflected that its use was favorable for the cure of the disease as first line therapy. It would also be necessary to compare its efficacy with other drugs.

The limitation of this study, although includes experiences from two distant institutions with similar populations and results, is the small sample size and the lack of comparison with other medical and surgical methods. However, similarly to Alfonzo Nuñez et al.,[6] we consider the treatment is effective in a high percentage of cases, has high adherence and almost no adverse effects, despite the difficult access due to its high cost of production. The absence of effects such as headache, hypotension, and other symptoms related to the use of nitrites or oral vasodilators is a highlight and contributed to high adherence to treatment. For these reasons, in patients with previous surgery for a fissure or other anal pathology, or with associated morbidity that contraindicates surgery, Tadalafil could be an excellent option despite requiring prolonged treatment.

CONCLUSION

Treatment of chronic anal fissure with topical Tadalafil is feasible and has a high healing rate. It is a safe method given that did not present any associated cardiovascular or other serious side effects.

It is a valid option for patients with contraindication to surgery or continence disorders.

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COMENTARIO

Gran parte de los paciente con fisura anal resolverán el cuadro clínico sin intervención quirúrgica, solo modificando hábitos o con la implementación de tratamiento médico, sin embargo existen diferentes tipos de tratamientos y opciones quirúrgicas para aquellos que no responden.

La mayoría de los tratamientos tienen como principal objetivo actuar sobre la hipertonía esfinteriana, principal factor implicado en la fisiopatogenia de la fisura anal. Para conseguir tal efecto se han implementado formulaciones con 2 o más drogas como principios activos, combinados con dosis fijas. Está demostrado que la combinación es beneficiosa cuando los ingredientes son incorporados de manera segura y efectiva en un número significativo de pacientes, y ofrece algunas ventajas sobre la administración simultánea de diferentes preparados de un solo componente activo, ya que mejora la compliance, eficacia y reduce los efectos adversos locales y costos.

Las preparaciones tópicas que contienen corticoides y anestésicos locales, son extensamente utilizadas para aliviar síntomas en diferentes patologías, especialmente la patología anal.

Los corticoides actúan mediante la unión a receptores esteroides reduciendo la síntesis de mediadores inflamatorios, la dilatación de capilares y el edema, por lo cual la mejora de los síntomas no es inmediata. En cambio, los anestésicos locales proveen alivio inmediato del dolor luego de su aplicación por lo que se logra un efecto sinérgico con la combinación de ambos componentes.

Si a esta combinación se le suma un principio activo como el tadalafilo (utilizado ampliamente para patología urológica), podría generar un mayor beneficio al actuar sobre la relajación de la musculatura esfinteriana, pero no puede atribuírsele directamente el éxito de la cura de la fisura

Si bien es una limitante del trabajo descripta por los autores, se aguardan trabajos que demuestren el efecto de la droga como único principio activo, esto podría lograrse con un grupo control.

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