ORIGINAL ARTICLE

Efficacy of diltiazem 2% rectal gel in the treatment of chronic anal fissure: a retrospective observational study

Eficacia de diltiazem 2% gel rectal en el tratamiento de la fisura anal crónica: un estudio observacional retrospectivo

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Abstract

Objective: *The aim of this study is to describe the effectiveness and safety of a magistral formulation of diltiazem 2% rectal gel as a treatment for chronic anal fissure.* **Material and methods:** *A retrospective observational study of all patients that began treatment with diltiazem 2% gel during 2019. The primary endpoint of the study was anal fissure healing. We also looked for differences in effectiveness between those initiating treatment and those who had been previously treated, long-term effectiveness through a 2-year follow-up and frequency of adverse effects.* **Results:** *Of the 166 patients included in the study, anal fissure healed in 72.9%. We detected adverse effects in 12 patients, the most common was local irritation. After 2 years of follow-up, 88% of patients did not relapse.* **Conclusion:** *In this study, use of topical diltiazem 2% has been shown to be effective and safe in the treatment of anal fissure and should be considered as the first line of therapy.*

Keywords: *Diltiazem. Fissure in Ano. Administration. Topical.*

Resumen

Objetivo: *El objetivo de este estudio es describir la efectividad y la seguridad de una fórmula magistral de diltiazem 2% gel rectal, como tratamiento de la fisura anal crónica.* **Material y métodos:** *Un studio observacional retrospectivo de todos los pacientes que comenzaron a ser tratados con diltiazem 2% gel durante el año 2019. La variable principal del estudio fue la cicatrización de la fisura anal. También se buscaron diferencias de efectividad entre aquellos que iniciaban el tratamiento y los que ya habían sido tratados previamente, efectividad a largo plazo mediante un seguimiento de 2 años y frecuencia de aparición de efectos adversos* **Resultados:** *De los 166 pacientes incluidos en el estudio, el 72,9% cicatrizaron la fisura anal. No detectamos diferencias estadísticamente significativas de efectividad entre los pacientes naive y aquellos que ya habían sido tratados. Detectamos efectos adversos en 12 pacientes, siendo el más frecuente la irritación local. Tras 2 años de seguimiento, el 88% de los pacientes no presentaron ninguna recaída.* **Conclusión:** *En este estudio, el uso de diltiazem 2% tópico ha mostrado ser efectivo y seguro en el tratamiento de la fisura anal y debería considerarse como primera línea terapéutica.*

Palabras clave: *Diltiazem. Fisura Anal. Administración Tópica.*

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Introduction

Chronic anal fissure is a lesion of the mucosa lining the anus in which there is an epithelial tear that persists for more than 6 to 8 weeks. It is usually located in the posterior raphe and the most common symptoms are pain during or after defecation that may last for minutes or hours, anal pruritus and rectorrhagia[1].

The etiology of chronic anal fissure is unclear. The traditional theory is that inadequate fiber intake generates hard stool, which, upon defecation, causes a tear in the anal mucosa[2]. However, though constipation may contribute to the development of chronic anal fissure, it is not the only factor involved. These patients have been found to have elevated resting internal anal sphincter pressure[2,3], which reduces posterior midline arterial flow, causing ischemia and thus entering a continuous cycle of pain, sphincteric spasm, and ischemia.

The goal of treatment is to reduce anal muscle tone and improve local vascularization, stopping the vicious cycle. According to the Clinical Practice Guidelines of the American Society of Colon and Rectal Surgeons[4], anal fissure should initially be treated conservative, combining pharmacological treatment (topical nitrates, calcium antagonists or botulinum toxin) with hygienic-dietary measures; such as the intake of a diet rich in fiber to avoid constipation, the use of fecal bolus softeners or warm water baths.

Lateral internal sphincterotomy (LIS) is a surgical procedure that reduces sphincteric hypertonia by sectioning the internal anal sphincter and is considered the treatment of choice in chronic anal fissure due to its high cure rate[5-7]. However, a percentage of patients develop irreversible incontinence after the procedure[6,8], so this technique is limited to patients with chronic anal fissure who have not responded to pharmacological treatment[9].

Calcium antagonists, such as diltiazem or nifedipine, are used as an alternative to LIS in the conservative treatment of chronic anal fissure, avoiding the risk of incontinence that this procedure can lead to. They are associated with a low incidence of adverse effects, the most frequent being headache or pruritus. They act by blocking L-type calcium channels in the muscle fibers of the internal anal sphincter, decreasing resting pressure and reducing sphincteric spasm, improving posterior midline blood flow[10,11].

Although there are pharmaceutical forms for oral administration, they usually produce systemic adverse effects such as orthostatic hypotension, nausea or headache. This has led to the development of topical forms for the treatment of chronic anal fissure. Jonas et al[12]. conducted a randomized clinical trial to compare the efficacy of topical versus oral diltiazem in the treatment of chronic anal fissure and observed that topically administered diltiazem was more effective, with 65% of patients resolving the fissure after 8 weeks of treatment versus 38% who received oral treatment.

To date, there is no topical pharmaceutical form of diltiazem approved by the Spanish Agency of Medicines and Medical Devices for the treatment of chronic anal fissure. Therefore, it is necessary to develop an extemporaneous preparation to be able to use a topical calcium antagonist in the treatment of this disease. This increases the risk of differences in composition and potency of the preparation when performed in different centers, which favors different results in patients receiving the same treatment.

The aim of this study is to describe the short- and long-term effectiveness and safety of a magistral formulation of diltiazem 2% rectal gel as a treatment for chronic anal fissure.

Material and methods

We conducted a retrospective observational study during 2019, which was approved by the local Drug Research Ethics Committee. We included all patients who attended the outpatient unit of a county hospital during the study period and who started treatment with a magistral formulation of diltiazem 2% gel (Table 1). All patients under 18 years of age, who did not have a diagnosis of anal fissure, if they received other additional topical treatment in the first 4 weeks of follow-up and those who had previously undergone a LIS were excluded.

The main study variable was anal fissure healing, considering as treatment failure those patients who did not achieve complete healing of the anal fissure, did not resolve the clinical condition or required additional topical treatment after the fourth week. We also looked for differences in effectiveness in naïve patients versus those who had been previously treated with topical diltiazem, appearance of adverse effects (headache, nausea, dizziness, local irritation or orthostatic hypotension) and long-term effectiveness, through a two-year follow-up of those patients who achieved complete healing, considering as relapse the appearance of symptoms suggestive of anal fissure. Other variables included in the study were

sociodemographic data (sex and age) and the number of containers collected.

The patients treated with diltiazem 2% were obtained from an internal registry of the pharmacy service. The clinical and sociodemographic variables were extracted from the patients' medical records using Abucasis® software. We used Microsoft Excel® software as a worksheet, while the statistical analysis was performed using IBM SPSS Statistics ver.23®.

We performed a statistical analysis using measures of centralization (median and mean), dispersion (interquartile range) and frequency. To determine differences in effectiveness between naive patients and those previously treated with diltiazem, we used Fisher's exact test.

To ensure patient privacy, a double-entry table was established that related the SIP number of each patient analyzed to a study number that was randomly assigned using the Excel® program. This list was kept in a locked cabinet in a password-protected worksheet and only the principal investigator had access to it.

No data that could identify the patient were recorded in the data collection sheet.

Table 1. Composition of topical diltiazem 2%

Components	Quantity
Diltiazem CLH	2g
Hydroxyethylcellulose	2g
Propylene glycol	10mL
Preserved water csp.	100mL

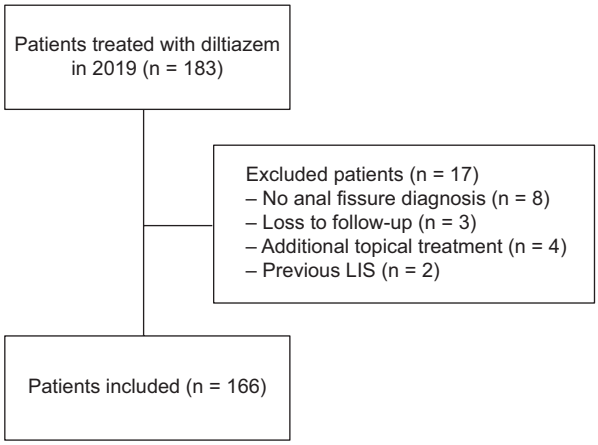

Figure 1. *Flow diagram of the patients included in the study.*

Results

Of the 183 patients studied, we excluded 17 patients from the study (Fig. 1). We included 166 patients (Table 2), of whom 81% had never been treated with topical diltiazem 2% and 19% had been treated previously.

Fifty-five percent were women, with a median age of 52 years (RIQ: 42-64).

Patients collected a median of 2 containers of diltiazem (range: 1-14) during treatment.

As for the primary study endpoint, anal fissure healing occurred in 72.9% of patients using topical diltiazem.

The anal fissure healed in 75.6% of the naive patients compared to 80.7% of those patients who had been previously treated with diltiazem. After performing Fisher's statistical test, we did not observe significant differences in the effectiveness of treatment between both groups (p = 0.329).

Regarding the 45 patients who did not heal their anal fissure, 53% received additional topical treatment, 18% were given botulinum toxin and 22% were treated with LIS.

We detected adverse effects in 12 naïve patients, and it was necessary to exchange the treatment in 11 of them for another topical drug. The most frequent was local irritation (42%), followed by headache (33%), dizziness (17%) and nausea (17%).

After 2 years of follow-up of the 121 patients who achieved complete healing of the anal fissure after completing treatment with topical diltiazem 2%, we observed that 88% of the patients did not present another episode of anal fissure, 10% suffered a relapse and 2% died.

Discussion

The aim of this study is to describe the efficacy and safety of the administration of an extemporaneous compound of Diltiazem 2% rectal gel in the management of anal fissure.

In anal fissure there is a tearing of the mucosa lining the anus, and it can be considered chronic when it persists for more than 6 weeks.

One of the most commonly used therapeutic options for chronic anal fissure is LIS, since it allows reducing the tone of the internal sphincter with a low rate of recurrence. However, several studies show that a high proportion of these patients develop

Table 2. Characteristics of patients treated with topical diltiazem 2%

	Naive (n = 135), n(%)	No Naive (n = 31), n(%)	Total (n = 166), n(%)
Women	72 (53)	19 (61)	91 (54,8)
Age (years), median (IQR)	49 (42-65)	52 (42-64)	52 (42-64)
No. of containers, median (range)	2 (1-14)	2 (1-10)	2 (1-14)
Healing	102 (75.6)	25 (80.7)	121 (72.9)
Therapeutic failure	33 (24.4)	6 (19)	45 (27.1)
Other topical treatment	21 (15.6)	3 (10)	24 (14.5)
Botox	5 (4)	3 (10)	8 (17.8)
LIS	7 (5)	3 (10)	10 (22.2)
ADR	12 (8.9)	0	12 (7.2)
Local irritation	5 (3.7)		5 (3)
Headache	4 (3)		4 (2.4)
Dizziness	2 (1.5)		2 (1)
Nausea	1 (0.7)		1 (0.6)

IQR: interquartile range; LIS: lateral internal sphincterotomy; ADR: adverse drug reaction.

irreversible fecal incontinence after surgery, which limits its use[6,8].

The use of calcium antagonists reduces sphincter hypertonia, improves local vascularization and constitutes an alternative to LIS, thus avoiding the risk of fecal incontinence. However, oral administration of calcium antagonists has been associated with the appearance of adverse effects such as nausea, vomiting and headache. For this reason, several formulations have been designed which allow their use topically, such as diltiazem 2% rectal gel that, thanks to its easy handling, acceptable efficacy and low incidence of adverse effects, is one of the most widely used options in the management of anal fissure.

In our study, 72.9% of patients treated with a compounded preparation of diltiazem 2% rectal gel achieved healing of anal fissure. These results are in agreement with a meta-analysis by Edward J et al[13]. which collected 9 clinical trials studying the efficacy of topical diltiazem 2%. Of the 379 patients included, 73.1% of patients successfully healed their anal fissure. Moreover, we observed no significant differences between those patients who were receiving the treatment for the first time and those who had already been treated.

The treatment was well tolerated by most patients. We observed the appearance of adverse effects in 7% of the patients, although all of them were mild, such as headache, nausea, vertigo or local irritation, the latter being the most frequent. It should be noted that all the adverse effects were detected in patients who had never been treated with diltiazem.

After two years of follow-up, 87.6% of the 121 patients who managed to heal their anal fissure did not experience any relapse. This implies that, taking into account the 155 patients included in the study, 68.3% were free of disease after two years. Nash et al[14]. obtained similar results when followed up for two years where 67.9% of the patients resolved the anal fissure after being treated with diltiazem.

In our experience, the results we have obtained in this study are similar to those of other investigators and support the use of topical diltiazem as first line in the treatment of anal fissure in order to avoid the need for LIS in the short term.

However, this study is not free of limitations. The observational design of the study and the absence of a control group makes it difficult to extrapolate these results to the population. In addition, the data were not obtained directly from the patients, but from the clinical history, which increases the risk of measurement bias.

Conclusions

In conclusion, in this study, treatment with topical diltiazem 2% has resulted in healing of 72.9% of anal fissures, with infrequent and mild adverse effects, so we consider it to be an effective and safe initial alternative to LIS in the treatment of anal fissure, thus avoiding the risk of fecal incontinence that this procedure implies.

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Conflicts of interest

The authors declare no conflicts of interest.

Ethical disclosures

Protection of humans and animals. The authors declare that the procedures followed were in accordance with the regulations of the relevant clinical research ethics committee and with those of the Code of Ethics of the World Medical Association (Declaration of Helsinki).

Confidentiality of data. The authors declare that they have followed their center's protocols on the publication of patient data.

Right to privacy and informed consent. The authors have obtained approval from the Ethics Committee for analysis and publication of routinely acquired clinical data and informed consent was not required for this retrospective observational study.

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