



Original article

Local treatment of a chronic anal fissure with diltiazem vs. nitroglycerin. A comparative study

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Aim: To assess the value of using smooth muscle relaxants drugs and assess the results of the topical use of 2% diltiazem as an alternative to 0.2% nitroglycerin in the treatment of chronic anal fissure (CAF).

Methods: Review of the CAF contained in a prospectively collected database of anal fissures including one hundred forty-five patients diagnosed with CAF and treated with standard measures (ST) in two consecutive periods. During the first period they were allocated alternatively to not receive further treatment (ST group) or to be treated with nitroglycerin ointment (NTG group). In the second period all were treated with local diltiazem (DTZ group). One hundred forty-five patients entered the study and 124 completed it.

Results: Initially there were significant differences in improvement rates (45% ST, 62.5% NTG and 80% DTZ, $P < .01$), but not in the cure rates (27% ST, 40% NTG and 39% DTZ) and the treatment was completed by 124 patients (85.5%). There were more side effects and more dropouts in the NTG group. In the subsequent follow-up for a median period of 25 months there were 25% recurrences and almost all responded to repeated medical treatment.

Conclusions: Smooth muscle relaxant drugs do not achieve a higher cure rate than the traditional measures used in CAF, but offer more symptomatic relief, providing an opportunity to avoid surgery. Topical diltiazem does not have the side effects of the nitroglycerin and is better accepted by patients.

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Tratamiento local de la fisura anal crónica con diltiazem vs. nitroglicerina. Estudio comparativo

R E S U M E N

Palabras clave:

Fisura anal crónica
Nitroglicerina tópica
Diltiazem tópico
Esfinterotomía química

Objetivo: Investigar el valor de la utilización de fármacos relajantes de la musculatura lisa y analizar los resultados de la utilización tópica de diltiazem 2% como alternativa a la nitroglicerina 0,2% en el tratamiento de la fisura anal crónica (FAC).

Métodos: Revisión de las FAC contenidas en una base de datos de fisuras anales con recogida prospectiva, incluyendo 145 pacientes tratados con medidas estándar en 2 periodos de tiempo consecutivos. Durante el primer periodo, se asignaron alternativamente a no recibir más tratamiento (Grupo EST) o a tratarse con nitroglicerina local (Grupo NTG). En un segundo periodo, todos fueron tratados con diltiazem local (Grupo DTZ). Se analizan los resultados después de un mes de tratamiento y las recidivas.

Resultados: Inicialmente hubo diferencias significativas en las tasas de mejoría (45% EST, 62,5% NTG y 80% DTZ; $p < 0,01$), pero no en la curación (27% EST, 40% NTG y 39% DTZ) y el tratamiento fue completado por 124 pacientes (85,5%). Ocurrieron más efectos adversos y más abandonos en el grupo NTG. En el seguimiento posterior, durante una mediana de 2 años, hubo un 25% de recidivas y casi todas respondieron al tratamiento médico reiterado.

Conclusiones: Aunque los fármacos relajantes de la musculatura lisa no consiguen más curaciones que las medidas tradicionales en las FAC, brindan más alivio sintomático, ofreciendo una oportunidad para evitar la cirugía. El diltiazem local carece de efectos secundarios y es mejor aceptado que la nitroglicerina. Las recidivas son frecuentes, pero responden bien al tratamiento médico repetido.

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Introduction

Chronic anal fissure (CAF) is a painful condition of the anal region of unknown cause. Classically it was thought to be caused by the trauma of hard faeces in patients suffering from constipation.¹ However, many patients with CAF do not suffer from constipation. Current data suggest that the cause is an ischaemic ulcer, due to high sphincter pressure.^{2,4} Laser Doppler flowmetry studies, combined with manometry,^{3,4} find that the perfusion of the anoderm is inversely related to maximum anal resting pressure (MARF), and is more reduced at the posterior commissure. Therefore, sphincter hypertony causes poor irrigation of the area, and, in consequence, a painful ischaemic ulcer. Anatomical, histological and angiographic⁵ studies support the ischaemic theory, but this theory does not explain why the tone of the internal anal sphincter (IAS) is increased. While this point is not clarified, any treatment for CAF must be aimed at reducing said hypertony.

Historically, the most usual way to achieve spasm relief is surgical treatment. Lateral internal sphincterotomy (LIS) has been shown, based on scientific evidence, to be the best surgical treatment for CAF.⁶ However LIS has a not unappreciable risk of incontinence, and its major complication is the escape of gasses, reported in 30%–45% of procedures.^{7–9} Alternative treatments have been used to achieve pharmacological relaxation of the IAS, such as reversible chemical sphincterotomy, and different smooth muscle relaxant drugs (SMRD), with varied mechanisms of action, have been used for this purpose, among them

nitric oxide donors and calcium channel blockers. Although there is no agreement in the literature on the role of these drugs,^{10–12} most recent studies support their use as first-line treatment, resorting to sphincterotomy when they fail.^{13,14} A metaanalysis of randomised studies, favoured the use of diltiazem in comparison with nitroglycerine due to the fact that it has fewer side effects.¹⁵

The aim of this study is to compare clinical results (clinical improvement and rate of cure) and adverse effects of two SMRD (diltiazem 2% and nitroglycerine 0.2%) in topical application, vis a vis each other and classical medical treatment for CAF. The null hypothesis is that these drugs have no effect whatsoever on improvement or cure of CAF.

Materials and methods

We carried out a retrospective revision of a database where the cases of anal fissure were registered prospectively and successively for 4 consecutive years in consultation at the General Surgery department of the Specialties Centre of Aldaya (Valencia), a dependency of the General Surgery Service of the University General Hospital Consortium of Valencia. The cases were divided into 3 groups: during the period 2005–2006, all the patients were alternatively assigned to a standard treatment group (ST), or associated treatment with topical nitroglycerine (NTG), whereas in the period 2007–2008 all the patients were treated with topical diltiazem (DTZ).

The three groups received standard medical treatment which consisted of fibre in the diet, abundant fluid intake,

Table 1 – Composition of topical treatments

Function	Nitroglycerine		Diltiazem	
	Composition	%	Composition	%
Emulgent (base)	NeoPCL O/W	25	NeoPCL O/W	25
Hydratant	Propylenglycol	5	Propylenglycol	5
Excipient	Distilled water	70	Distilled water	68
Active ingredient	Nitroglycerine hydrochloride	0.2	Diltiazem hydrochloride	2

Table 2 – Epidemiology and clinical data

	Standard	Nitroglycerine	Diltiazem	Value of P*
n	38	40	46	
Age				
Mean (SD)	45 (13)	49 (15)	49 (13)	.3
Range	20–68	16–75	20–79	
Sex (M/W)	14/24	21/19	24/23	.3
Proctalgia/anal itching (%)	38 (100)	40 (100)	46 (100)	
Rectorrhagia (%)	31 (82)	34 (85)	34 (74)	.1
Anal pruritus (%)	4 (10.5)	5 (12.5)	3 (6.5)	.2
Single fissure (%)	35 (92)	36 (90)	44 (96)	.6
Posterior location (%)	29 (76)	30 (75)	37 (80)	.7
Constipation (%)	17 (45)	16 (40)	19 (41)	.7
Evolution > 3 months (%)	22 (58)	22 (55)	32 (70)	.4

M indicates man; SD, standard deviation; W, woman.
*Pearson's chi square test

Plantago ovata, analgesics, hip baths and, in cases with constipation, lactulose or paraffin oil. The patients in the NTG and DTZ groups had additionally 3 topical applications a day with nitroglycerine 0.2% and diltiazem 2%, respectively (Table 1).

During the first visit, we collected, according to the established protocol, demographic data and data on symptoms, evolution and exploration. The patients were re-assessed at least once during the second month of treatment. And the clinical results registered (improvement, disappearance of symptoms and cure), as also the possible side effects of the treatment and patient adherence. Improvement was registered when the patients said they had improved (subjective criteria). Cure meant disappearance of the fissure, with absence of symptoms and total healing seen on consultation (objective criteria).

It was considered that treatment had failed when the patients said they had not improved and objectively the fissure was seen to persist. Failures were usually sent to surgery, with the exception of special cases (symptoms tolerated, high risk of incontinence or express wishes of the patient), and in these treatment was continued for an additional period of time or alternative medical treatment was used. It was considered that treatment had been successful when the patients said they had improved clinically. If the improvement was associated with fissure persistence,

treatment was continued for another 2 months. Follow-up consultations were ended when one of 2 events occurred: cure or referral to surgery.

For the retrospective analysis, only idiopathic CAF of typical clinical presentation were taken into account. We did not include atypical proctalgias, fissures with no pain, fissures associated to inflammatory bowel disease or those that did not comply with chronic criteria.

We considered CAF those with an evolution longer than 6 weeks, a history of previous attacks of proctalgia or local signs of chronicity.

In a second phase, we reviewed the electronic history only of those patients that had been cured, with the aim of detecting relapses. This review was carried out using the Ambulatory Information System (AIS) (Project Abucasis II, Care Module, Integral Patient Management), where all medical contacts in the area are registered.

Data on all the anal fissures was collected in an Access Data Base (Microsoft Corporation, Washington, District of Columbia, USA). The statistical analysis of the CAF was done using an SPSS computer program version 12.0 for Windows (SPSS Inc. Chicago, Illinois, USA), carrying out descriptive analysis and comparisons. Qualitative variables were compared using Pearson's chi square test. Quantitative variables were compared by Analysis of Variance (ANOVA), having previously ascertained that the data corresponded to

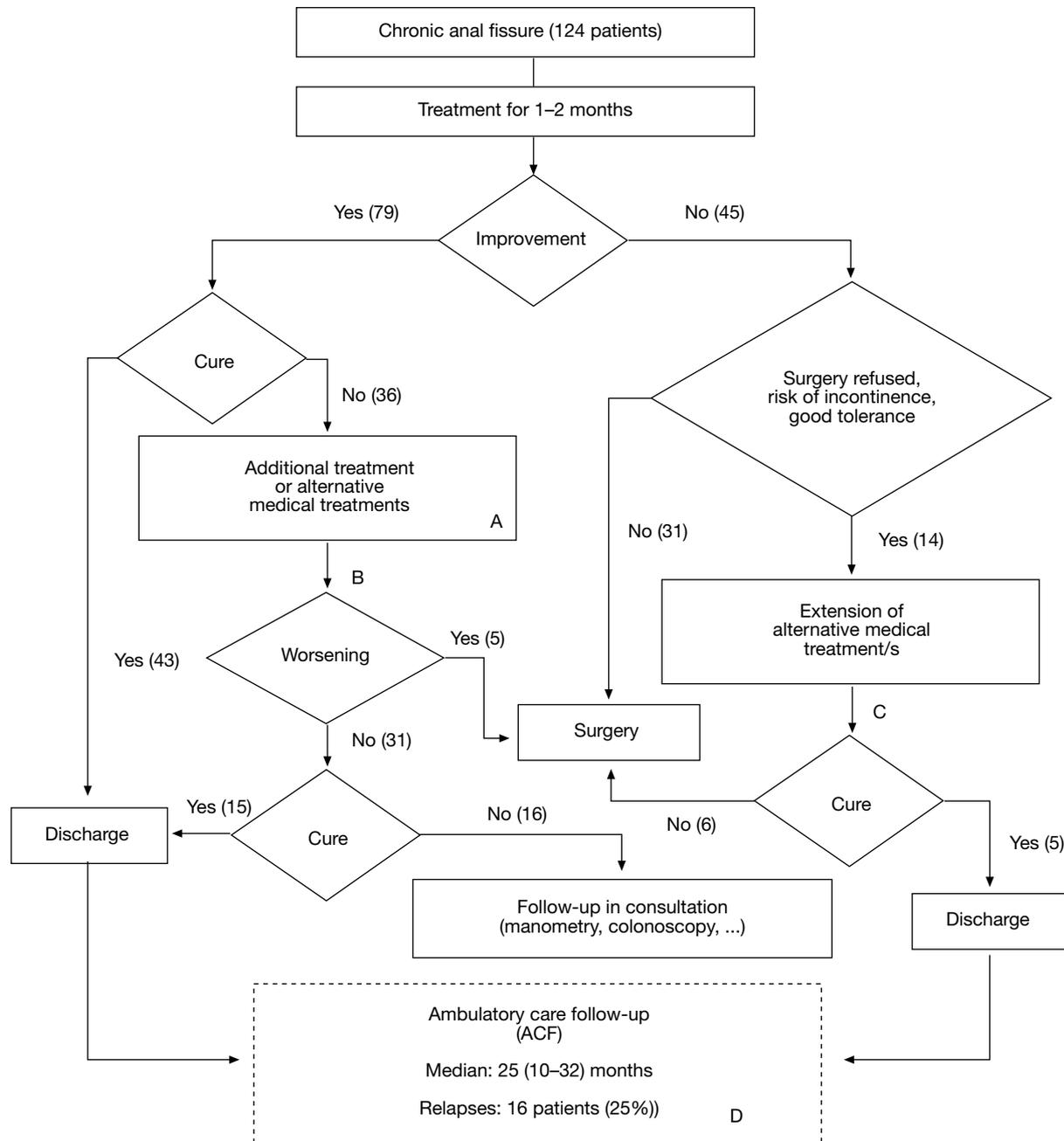


Figure. Action plan and overall results of improvement or cure. The total number of patients in category is in brackets. Alternative medical treatments: standard → nitroglycerine, nitroglycerine → diltiazem. B) Follow-up consulting for a median of 4 (2-7) months. C) Three patients who did not respond to initial medical treatment did not return to consultation after prolonging or changing their treatment. C) The AIS made it possible to review, retrospectively, all the medical contacts of the 64 patients that were cured, which made it possible to detect relapses.

a normal distribution (Kolmogorov-Smirnov test). Values of $P < .05$ were considered statistically significant.

Results

The groups had 42 cases in the ST group, 47 in the NTG group and 56 in the DTZ group. The 21 patients who did not come

to follow-up were excluded, and the analysis was performed with the remaining 124 (38 ST, 40 NTG and 46 DTZ).

All the groups were homogeneous in age, sex and symptoms, location of the fissure, intestinal habits and time of evolution (Table 2).

In Figure it is possible to see the general scheme of action and the overall results (not grouped) of success or failure of treatment.

Table 3 – Initial response to treatment: comparative results

	Standard	Nitroglycerine	Diltiazem	Value of P*
No.	38	40	46	
Improvement (%)	17 (45)	25 (62.5)	37 (80)	<.01
Asymptomatic (%)	10 (26)	15 (37.5)	17 (37)	.3
Cure (%)	10 (26)	16 (40)	18 (39)	.4
Headaches (%)	0 (0)	11 (27.5)	0 (0)	<.001
Non-compliance/abandonment of treatment (%)	0 (0)	9 (22.5)	0 (0)	<.001

*Pearson's chi square test.

Assessment was carried out during the first 2 months of treatment. Significant differences were seen between groups in clinical improvement and side effects, but not in cure rates (Table 3). It was considered that treatment had been successful in 79 patients that improved, and it failed in the remaining 45. Clinical improvement was significantly greater in the DTZ group than in the ST group (80 vs 45%; $P=.001$), whereas the NTG group was intermediate with 62.5% improvements, but not statistically significant in comparison with the other 2 groups. However, a complete cure was obtained only in 43 cases and there were no significant differences between groups.

The group of 36 patients with persistent fissure that had improved initially was followed up in consulting rooms, until complete cure was seen or until they worsened and were sent to surgery. After a median period of follow-up (interquartile interval) of 4 (2–7) months, 15 were cured (42%) and only 5 (14%) had worse symptoms and required sphincterotomy.

Of the 45 patients in which initial treatment failed, 31 were sent to sphincterotomy, and 14 had additional treatment or received alternative medical treatments (fissure well tolerated, high risk of incontinence and/or refusal to undergo surgery). Of these 14 patients, 5 achieved complete cure.

All the medical contacts of the 63 patients who finally were cured (AIS module of care) during the median (interquartile interval) of 25 (10–32) months from the moment of cure, until relapse or the last day in which the patient came into medical consultation in the area. The treatment applied to relapses and its results were investigated. There were 16 relapses (25%), and the median time to relapse from the moment of cure was 8.5 (3.5–19) months. There were 4 relapses in the ST group, 6 in the NTG group and 6 in the DTZ group; the differences between groups were not significant. In 2 cases of relapse it was not possible to know what treatment was applied, another was pending assessment by the surgeon at the time of review, 3 were sent to surgery with no previous attempt to carry out conservative treatment, 2 were treated with diet-hygiene measures and cured, 3 were treated with nitroglycerine and of these 2 cured, and 5 were treated with diltiazem and all cured. Therefore, 7 of the 8 relapses that were treated with SMRDs cured.

Discussion

Acute anal fissures tend to cure with simple conservative measures,^{16,17} whereas CAF usually need other types of

treatment or surgery.¹⁷ There is no agreement in the literature on the criteria to define CAF,¹⁶ so we used the time of duration of symptoms and the signs of chronicity seen on exploration. Most authors arbitrarily use a 6 week time of evolution as a selection criterion. Following Nelson's directives in his review of Cochrane,¹⁹ we have used both evolution and morphological data to select CAF. We consider the ailment is chronic when there is a history of pain of more than 6 weeks duration or pain of less duration, but with similar episodes in the past, or with signs of chronicity.

Nitroglycerine is a donor of the main IAS inhibiting agent, nitric oxide.²⁰ The excellent results seen in the years 1996–1997 in several controlled assays with the topical application of 0.2% nitroglycerine, with a cure rate of about 2/3 of all CAF^{21–23} and clinical improvement of up to 100%,²¹ were not corroborated by subsequent studies in which the cure rate seen was less than 55%,^{16,24–28} similar to what was obtained with placebo^{16,27} and worse than with sphincterotomy,²⁶ in addition to the observation of high rates of headaches (up to 84%),²⁹ non-compliance (11%)²⁹ and relapses at 6 months (27%).²⁴ The lack of efficacy could be related to the short duration of action at the usual concentration and dose, which is insufficient to maintain permanent relaxation of the IAS during its application.³⁰ Our results agree with the ones seen in these studies, since we obtained a cure rate of 40%, which is not significantly better than 27%, the cure rate obtained with diet and hygiene measures and we had an important rate of headaches (27.5%) and non-compliance (22.5%).

Diltiazem promotes smooth muscle relaxation by blocking calcium channels. Topical diltiazem reduces maximum anal resting pressure (MARF) by approximately 28% for 3–5 hours.³¹ High rates of cure of CAF have been reported, comparable to those seen with nitroglycerine,^{18,28,32–35} with infrequent side effects.^{19,32–34,36} This drug is well tolerated and treatment is rarely abandoned.^{33,35} Randomized controlled studies comparing diltiazem with nitroglycerine have shown the superiority of diltiazem, with a lower incidence of side effects, and with similar efficacy^{32,37} or greater³⁸ clinical efficacy, which would support its use as first-line treatment. There is also data that suggests that half or more fissures refractory to treatment with NTG can be cured by applications of diltiazem,^{34,36,39} avoiding the need for surgery in up to 70% of cases.³⁹ Many authors apply it twice a day,^{35,37} this interval between applications could be too long, if we consider that the effect lasts 3–5 hours, we therefore agree with those authors that apply it 3 times a day.^{18,28,34} We have seen a

high rate of clinical improvement during the first 2 months of treatment that has reached 80% in patients that had no further symptoms or were slightly symptomatic; however, if we consider complete cure, this was only achieved by 39% of cases, and there was no statistically significant difference with ST (27%) or the NTG group (40%).

Bernal et al²⁸ have pointed out that the dissimilar clinical results obtained by different authors could be due to the composition of the excipients that accompany the active ingredients. We also believe that the subjectivity of clinical assessment could be a contributing factor and different views on what are good results of treatment. Some consider that successful treatment is complete cure. This is the most objective and standard criteria and a good measurement of results.¹⁹ For others, success is the disappearance of anal pain and/or fissure^{18,28} or simply relief from pain and patient satisfaction.³⁵ We have considered both clinical improvement and cure when measuring results. Even considering that clinical improvement is less objective, we think it is adequate, since this treatment is considered an alternative to surgery and we can consider it effective when the relief from pain has been sufficient to make sphincterotomy unnecessary. If we consider that success is only a complete cure of the fissure, we would have to consider patients who do not require additional treatment as failures. Placer et al¹⁸ concluded in his study that early relief of pain was a predictive factor for the final cure of the fissure. In our series, after a median follow-up period in consultation of 4 (2-7) months, 15 (42%) of the 36 fissures that had initially responded to treatment had cured, whereas only 5 (14%) worsened or required sphincterotomy.

One of the main criticisms of medical treatment of CAF has been the high percentage of recurrences, of up to 59% in a mean 2 year follow-up.³⁵

We can also consider that pharmacological treatment simply delays surgery and that many, if not the majority of patients that receive diltiazem as primary treatment of their CAF will subsequently require further treatment.³⁵ In our study we found 25% relapses. We agree with the authors that hold that relapses usually respond to repeated medical treatment,³³ it being possible to avoid surgery in most cases. In our series, most patients that had a relapse and were treated with SMRD responded to treatment.

We believe that this conservative approach when faced with relapses should be used with patients who are willing to carry out repeated treatments.

In conclusion, SMRD do not have a better rate of cure than conventional measures for the treatment of CAF, but they achieve significantly greater symptomatic relief and offer a possibility of avoiding surgery. Relapses are a frequent problem, but they usually respond satisfactorily to repeated medical treatment. Local diltiazem does not have the side effects nitroglycerine has and it has a higher rate of patient compliance.

The good results obtained in this study have encouraged us to continue using topical diltiazem as first-line treatment of CAF and as repeat treatment in recurrent CAF in patients who do not accept surgery or who have a high risk of postoperative anal incontinence.

Conflict of interest

The authors state they have no conflicts of interest.

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