Long-term follow-up of chronic anal fissure (CAF) on diltiazem 2% using a telephone questionnaire. Do results change?

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ABSTRACT

Introduction: Calcium channel blockers have an excellent effectiveness in the conservative management of chronic anal fissure (CAF).

Objectives: To assess the long-term results of management with diltiazem 2% ointment using a telephone questionnaire.

Methods: A descriptive, retrospective study from March 2004 to March 2011 in patients with CAF on diltiazem 2%, 3 applications daily for 4-6 weeks. Starting at 12 months a questionnaire was administered over the phone by medical staff outside the surgery department to record socio-demographic data, predominant manifestations, and response to diltiazem on a 5-point scale measuring symptom relief (1 = poorest, 5 = best). Patients with therapy failure were referred to surgery.

Results: The study was completed for 166 patients with a mean age of 54.1 years. CAF was posterior in 82.3% of subjects. Diltiazem tolerability was excellent with only 4 adverse event cases (3 skin irritation, 1 hypotension). We obtained symptom relief in 62.1% of patients and CAF healing in 51.2%, and referred 33.7% (3 skin irritation, 1 hypotension). We obtained symptom relief in 62.1% of patients and CAF healing in 51.2%, and referred 33.7% (3 skin irritation, 1 hypotension). The questionnaire showed that 74.1% of patients had used only 2 applications daily, and that results were better with an increased number of applications, albeit without statistical significance.

Conclusions: The telephone questionnaire showed symptom relief for 62% and healing for 51.2% of patients with CAF on diltiazem 2%, which should be considered first-choice for the conservative management of this condition.

Key words: Chronic anal fissure. Diltiazem 2%. Telephone survey.

INTRODUCTION

Chronic anal fissure (CAF) is a condition with a high prevalence amongst anorectal disorders, and causes severe pain and quality of life impairment. Several studies have shown the virtually constant presence of hypertension at the internal anal sphincter (IAS), which compromises blood supply in both the anterior and posterior commisures (1,2), and would be responsible for anal fissure chronification. Thus, the goal of fissure management is focused on reducing said hypertension.

Calcium antagonists are considered to provide excellent effectiveness in the conservative management of chronic anal fissure, with a similar effect to that of nitrates and fewer side effects (2-4) –the paper by Puche et al. already assesses such features in the short term, and reveals better results as compared to nitrates (5).

During the period 1999-2004 we carried out a comparative study of the response to topic nitroglycerin (NTG) 0.2-0.3% and diltiazem 2%. Diltiazem was initially superior in cure rate (78.8% vs. 51.5% and 56% for NTG 0.2% and 0.3%, respectively). Puche et al. (5) assessed these characteristics short-term, and also obtained netter results compared to nitrates, not so much in cure rate, which was similar, as in the percentage of adverse events and treatment discontinuations, both higher in the nitrates groups.

Our favorable results led us to consider even the possibility that the excipients used in the formulation could have improved absorption, as our preparation differed from that used in the randomized study by Plácer et al. (7), and we had demonstrated better initial results in our study (8). Given that absorption is erratic and a subjective component is present when assessing the response of chronic anal fissure to medical treatment, a comparative study between the excipients in the diltiazem ointments used by Plácer and us would have been desirable to reveal any scientific grounds in this regard. In 2013, the team led by Shah (9) showed in a study performed in the USA that a huge proportion of the diltiazem preparations prescribed to patients with anal fissure formulated in various pharmacies in a big metropolitan area exhibit significant differences in strength and composition, which favor result disparity even for patients receiving the same sort of therapy.

In this paper we set the goal of assessing the long-term results of topical diltiazem 2% ointment, of testing its effec-
tiveness for the conservative management of CAF, and of see-
ing whether our good short-term results are thus ratified (8).

MATERIAL AND METHODS

A descriptive, retrospective study was designed involving
the period of time from March 2004 to March 2011. A telephone questionnaire was developed by practitioners
outside the surgery department (family practice residents)
based on a data collection sheet from the questionnaire by
Fernández García et al. on the effectiveness and safety of
topical diltiazem 2% (11) (Fig. 1). During the telephone
interview information on demography as well as on pre-
dominant symptoms and associated manifestations was
obtained (Table I). Surgical history, mainly in the anal
region, was also reported.

We defined chronic anal fissure as any fissure with a
minimal duration of 6 weeks with typical manifestations
and findings.

Once diagnosed patients were started on diltiazem
2% ointment three times a day (Table II) for 4-6 weeks,
as approved by the Hospital Pharmacy Committee. All
patients signed an informed consent prior to diltiazem 2%
dosing as it was a magistral formula prepared in our site
(Fig. 2). A therapy collection data was completed for the
pharmacy records, and patients were given an information
sheet on the medical management of CAF. Therapy was

| Table I. Clinical and epidemiological data |
|-----------------|-----------------|
| n               | 166             |
| Sex (males/females) | 81/85       |
| Mean age (range)  | 54.1 ± 15.1 (R: 16-86) |
| Manifestations   |                 |
| Proctalgia (%)   | 132 (79.5)      |
| Rectorrhage (%)  | 89 (53.6)       |
| Anal pruritus (%)| 86 (51.8)       |
| Single fissure   | 98 (59)         |
| Fissure + hemorrhoids | 62 (37.3) |
| No fissure observed | 16 (9.6%)    |
| Site             |                 |
| Anterior (%)     | 27 (14.9)       |
| Posterior (%)    | 149 (82.3)      |
| Dual (%)         | 5 (2.8)         |

Fig. 1. Questionnaire designed for the assessment of diltiazem response over the telephone.
extended for 4-6 additional weeks in case of improvement even in the absence of fissure healing (according to an examination performed at the doctor’s office). Otherwise a surgical procedure was considered.

Fissure healing was again checked with a clinical examination at one year after treatment completion.

On discharge as outpatients, subjects were followed up over the telephone starting at 12 months after treatment onset by family medicine (FM) residents then in our department, always under the supervision of a specialist. To this end CAF cure was considered to involve absence of pain and/or fissure. Fissure persistence or cure was thus acknowledged, with internal lateral sphincterotomy (ILS) being indicated in the former case. When in doubt, the patient was scheduled for a new revision. Patients previously operated upon for anal fissure were excluded from the study.

A sample descriptive analysis was carried out to provide the distribution of qualitative variables; quantitative variables were analyzed using measures of both centralization (mean) and dispersion (standard deviation, range). A p value < 0.05 was considered significant. Data were analyzed using the SPSS for Windows V 12.0 statistical package (SPSS Ibérica, Madrid, Spain).

RESULTS

The study group was made up by 181 patients, 90 males and 91 females. Mean age was 54.1 ± 15.2 years (range: 16-86). Nine patients were excluded because of acute anal fissure and 6 because of non-compliance, hence 166 (91.7%) subjects completed the study. Predominant manifestations included pain in 79.5% of cases. We found rectorrhage in 53.6% and pruritus in 51.8%. Physical examination revealed an anal fissure in 150 subjects (90.3%), this being associated with hemorrhoids in the remaining 62 patients (37.3%). Fissure site was posterior in 82.3%, anterior in 14.9%, and dual in 2.8% of patients.

Of all 166 patients, 7 (4.2%) had undergone prior anorectal surgery (excluding surgery for anal fissure).

Table II. Diltiazem 2% ointment formula

<table>
<thead>
<tr>
<th>Ingredient</th>
<th>Percentage</th>
</tr>
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<tbody>
<tr>
<td>Diltiazem CLH</td>
<td>2 g</td>
</tr>
<tr>
<td>Neo PCL O/W self-emulsifying base</td>
<td>25%</td>
</tr>
<tr>
<td>Propylene glycol</td>
<td>5%</td>
</tr>
<tr>
<td>Acqua conservans</td>
<td>70%</td>
</tr>
</tbody>
</table>

After 1 year on treatment subjects underwent a new outpatient examination to confirm proper fissure healing. It is from this time point on that the telephone questionnaire was administered. Patients were deemed to be cured or sufficiently improved when no manifestations or only mild discomfort with no impact on daily activities were reported.

During telephone follow-up the extent of symptom relief was assessed with a 5-option scale: Very good, good, moderate, poor, poorest. A total of 74 (44.6%) patients reported their perceived outcome as very good, 29 (17.5%) as good, 28 (16.9%) as moderate, 26 (15.7%) as poor, and 9 (5.4%) as poorest. Up to 66.3% (110 patients) required no surgery; 85 cases (51.2% of total) were defined as cured, and 81 (48.8%) were deemed not cured. Symptom relief was seen in 103 (62.1%) subjects. A total of 56 (33.7%) patients were referred to surgery by internal lateral sphincterotomy (Fig. 2). There is a good correlation between patients reporting grade-4 (good) and grade-5 (very good) symptom relief and patients requiring no surgical procedure (62.1% vs. 66.3%).

Table III shows the number of diltiazem ointment applications used. The fact that cure percentages increase with number of applications may be clearly seen; this is also the case for better symptom relief (grades 4 and 5) and a lower proportion of patients referred to surgery, albeit with no statistical significance.

DISCUSSION

Chronic anal fissure is defined as an anodermal injury, distal to the dentate line, which may be classified as acute or chronic, a duration of 6 weeks being accepted as the time limit criterion (9,11,13). Different sites regarding the anterior or posterior midline (less than 1%) should raise suspicion for associated conditions (Crohn’s disease, STD, TB, cancer…) (14-16). Patients included in our study met such characteristics, as 82.3% had a posterior lesion.

Nearly all authors (6,10,12-14) agree that anal fissure management should be directed to reduce IAS pressure,
since patients seek clinical improvement rather than fissure healing.

Most of our patients had pain as their primary symptom, as is also reflected by other authors (5,11,14).

Different medical and surgical methods (10-15,17) have been studied in clinical trials to establish treatment regimens for CAF. The European Society of Coloproctology (ESCP) issued guidelines including a therapeutic algorithm involving all management options (18). Recently a preliminary study was reported that purportedly assesses the results of sacral nerve stimulation using transcutaneous electrostimuli on the posterior tibial nerve as an adjuvant to conventional medical therapy for CAF (19).

ILS, whether open or closed, has been traditionally accepted as the gold standard for the management of anal fissure, with a high percentage of cures that may exceed 90% according to various series (5,18,20). Despite a low relapse rate, the main problem with this technique is incontinence, which may develop after the procedure (14,18,21). This is why a number of studies have been carried out in search of the best conservative therapy for chronic anal fissure including a transient relaxation of the IAS. Topically used calcium channel blockers (diltiazem 2% ointment with 2 applications daily) are amongst these, with good short-term and mid-term results in the studies performed so far, comparable to those obtained with topical nitroglycerin (NTG) (2 applications daily of NTG 0.2-0.4% ointment) but with fewer side effects (3,10,22-27), headache and anal pruritus being most common (6,23).

In our study, treatment adherence was highly satisfactory, with only 6 subjects discontinuing therapy and 4 subjects developing adverse effects (which is in contrast with the paper by Fernández (11), who reports side effects in up to 30% of subjects), which also demonstrates the fine tolerability of diltiazem. Doubt arises whether the fluid, stringy vaseline excipient used in the study may be responsible for the higher prevalence of side effects, with 18.6% of allergic reactions and burning.

From the results listed in table III it is clear that the higher the number of daily applications, the higher the success rate and the lower the number of patients referred to surgery. Unfortunately, most subjects included belonged in the active population, and only managed to apply the ointment twice daily because of their work. However, we consider that the reason why statistical significance was not reached is simply our reduced sample size.

Assessing the long-term results of therapy with diltiazem 2% was of primary importance since short-term outcomes are scarcely reliable given the relapses seen after conservative management (23). In the study by Nash et al. (26), after following up for 2 years 112 patients on diltiazem 2% for 6 weeks, over one half (59%) needed a subsequent medical or surgical treatment. We obtained a cure rate of 41.3% in our follow-up of patients after 12 months. Another 31.8% (44 patients) later required surgery, and the rest said they were satisfied and claimed no surgery. We interpret this fact as a bias that may result from various reasons, the main one being fear of potential incontinence, as reported above.

The questionnaire administered shows that the initial results observed and reported by us in 2006 do not persist over time. Then 78.8% of patients were categorized as cured, with significantly better results as compared to those seen in subjects on nitroglycerin. We believe that questionnaires over the phone add a superior confidentiality component when administered by staff outside our department, as this allows a higher degree of sincerity in patients facing a short, simple set of questions. In comparison with 78% as initially reported by us we now obtained 66.3% of “overall improvement” (cures plus clinical improvement without surgery). When measuring absolute cure rates, our results do demonstrate a significant decrease.

We understand that our study has a primary limitation, namely the inability to administer all patients exactly the same therapy, even if these are divided into groups according to number of applications, as patients dose the ointment themselves without us really knowing how. These render results not as accurate as they should be. Also, we must reflect what patients report when answering to the telephone questionnaire, and trust their sincerity.

Our previously reported results could not be ratified. However, after seeing the results of this questionnaire we still feel that the conservative management of chronic anal fissure with diltiazem 2% ointment is a safe option with an acceptable cure rate, which should be considered first-choice in this setting.

### REFERENCES