

## DILTIAZEM 4% TOPICAL FOR CHRONIC ANAL FISSURE

C. Duta<sup>1</sup>, C. Neamtu<sup>2\*</sup>, E. Hordovan<sup>1</sup>, D. Barjica<sup>1</sup>, A. Salim<sup>1</sup>, B. Totolici<sup>2</sup>

<sup>1</sup>, „Victor Babes” University of Medicine and Pharmacy Timisoara, Second Surgical Clinic, Timisoara, Romania

<sup>2</sup>, „Vasile Goldiş” Western University of Arad – Faculty of Medicine, Pharmacy and Dental Medicine, Arad, Romania

**ABSTRACT.** Anal fissure is a relatively common disease in the population. It is estimated that ~ 10-15% of the population is affected by this problem. If an anal fissure healing period is beyond 6 weeks, we can say that it is a chronic anal fissure. **Material and method:** it is a retrospective study of three years – 2010 – 2012, on 478 patients from Medvarix Clinic in Timisoara. **Results:** This study demonstrated the efficacy of local topical diltiazem 4%, because 73% of patients with anal fissure who addressed our proctological clinic were cured and 15% of them showed improvement during the follow-up of 18 months. Recurrence after this period was 19% . **Conclusions:** With this study we want to demonstrate the importance of local topical treatment with diltiazem 4%, as alternative treatment to internal sphincterotomy with a high risk of anal incontinence as demonstrated by several studies.

**KEYWORDS:** anal fissure, local, topical treatment, diltiazem

### INTRODUCTION

According to Antropoli pathologies of the anal canal are extremely common (Kirsch J et al., 2004; Antropoli C et al.1992), about 30–40% of the population suffers from proctologic pathologies at least once in their lives and 10-15% of them suffers from anal fissure (Corman M et al.,1998). Fissures occur most often in the posterior midline in both men and women, although anterior midline fissures are more commonly seen in women. Chronicity of a fissure is characterised by a duration greater than 6 weeks with fibres of the internal anal sphincter visible at the bottom of the fissure. (Bhardwaj R. et al.,2007)

Secondary changes occur in chronic fissures like sentinel tag, hypertrophied anal papilla, induration of the edge of the fissure, and/or relative anal stenosis secondary to spasm or fibrosis of the internal sphincter. ( Jan Rakinic et al.,2007)

#### Conservative measures

The initial approach in the treatment of anal fissures is non-operative.

#### Nonsurgical methods

Smooth muscle relaxation is an effective treatment for chronic anal fissure and has advantages over surgical treatment in avoiding longterm complications. Smooth muscle relaxation has been tried using a variety of agents (De Nardi P et al., 2006; Kassai M et al., 2001).

- **Calcium antagonists**

**Nifedipine** is a dihydropyridine calcium-channel blocker which inhibits calcium ion entry through voltage-sensitive areas of vascular smooth muscle and myocardium. Topical and oral formulas of nifedipine have been evaluated but not used in routine clinical practice.( R. Bhardwaj et al.,2007)

**Diltiazem**, a non-dihydropyridine calcium-channel blocker, also affects vascular smooth muscle relaxation and dilatation. Topical 2% diltiazem reduces maximum resting pressure by approximately 28% and this effect lasts 3–5 h after application. Side effects are minimal with diltiazem and include perianal dermatitis, itches, headache, drowsiness, and mood swings. (R. Bhardwaj et al.,2007)

- **Nitrates**

**Nitroglycerin** ointment in proportion of 0.2 to 0.5%, applied directly to the internal anal sphincter, reduces pain and increases blood flow in the anal mucosa, thus helping the healing of the fissure (Ward D.I.et al., 2000; Keith B.K et al., 2001; Cundall J.D et al., 2001).

Unfortunately, the adverse effects of nitrates restrict their use, mentioning among them headaches and vertige, which are relatively common (up to 38% in some studies) (Utzig MJ et al., 2003; Jonas M et al., 2001; Dawas P et al., 1999). The nitrate most used is nitroglycerin.

**Glyceryl trinitrat**

Some of the patients had discontinued GTN prematurely because of headaches.

- **Botulinum toxin**

When all conservative treatments are exhausted, options may appeal to botulinum toxin. The precise anatomical position in which to inject botulinum toxin has been a matter of some debate as comparable healing rates are seen when injected into both internal or external sphincter. It has been shown that botulinum toxin reduces the internal sphincter tone through its effect on the sympathetic nervous system (R. Bhardwaj et al., 2007).

- **Lateral internal sphincterotomy**

Represents a surgical technique to cure anal fissure. It has been favored by most of the surgeons, because it offers long-lasting relief in sphincter spasm (Gupta PJ et al., 2004; Gupta PJ et al., 2002). The most preferred options are the manual dilatation with radiosurgery and subcutaneous lateral internal sphincterotomy. Traditionally, lateral internal sphincterotomy was considered as the gold standard treatment for chronic fissures, but it permanently weakens the internal sphincter and may lead to anal deformity

and incontinence in 8–30% of patients (Garcia-Aguilar J et al., 1996; McCallion K et al., 2001). Therefore, recently, nonsurgical treatment modalities have been developed.

**MATERIAL AND METHODS**

478 patients with anal fissures were studied, that addressed to our clinic in the last 3 years, between 2010 and 2012, a typical proctologic clinic. Distribution of patients per years was 183 patients in 2010, 197 patients in 2011 and 98 cases in 2012. First choice treatment in the last decade was local topical Diltiazem 4%. Duration of treatment was an average of 8 weeks. We recommended the application of diltiazem ointment topically 4%, twice a day. Some of the patients were treated with ointment twice daily in our clinic by health professionals. Follow-up period was an average of 18 months. Most patients were around the age of 36 years (range 3 years - 82 years). An approximate involvement of the two sexes with anal fissure was a women/man ratio of 2/1 (Fig.1). The most affected age category was the fourth decade, followed by the fifth, the least involved being the 2 extremes.

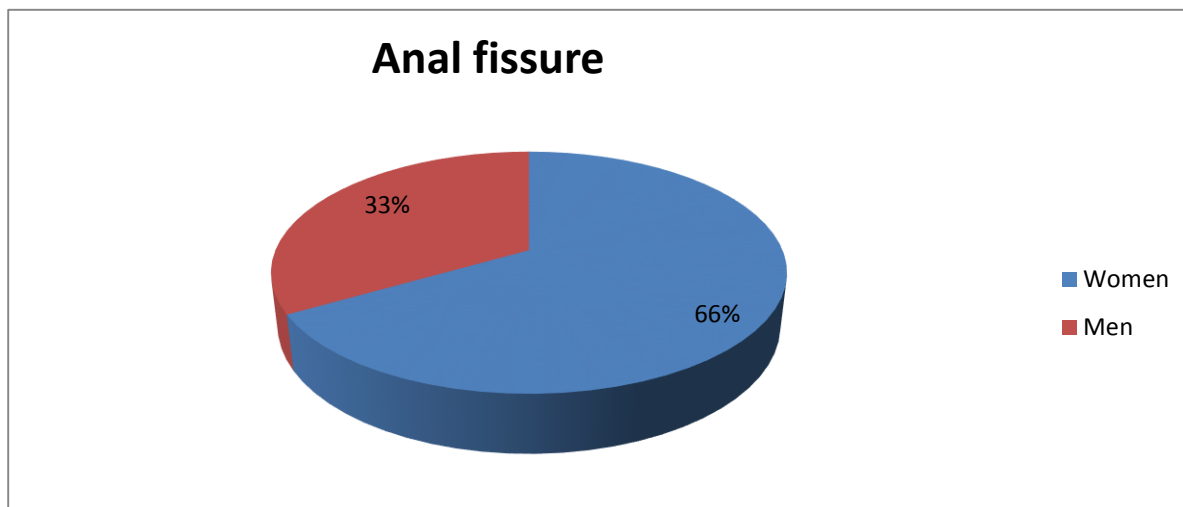


Figure 1. Involvement of the two sexes with anal fissure

**RESULTS**

We analyzed the healing of the anal fissure after de treatment with diltiazem 4%, in the follow-up period of 18 weeks. The clinic results were good, the anal fissure cure rate was 73% of cases after 8 weeks of treatment (Fig.2). Patients with resistant anal fissure despite the treatment were 12% of cases, but the symptoms were improved in

15% of patients. After 18 weeks of follow-up 19% of patients returned in our clinic for recurrent symptoms.

Among patients who presented to our clinic the most frequent fissure was the posterior - 90%. Both anterior and lateral fissure represented 5% (Fig.3).

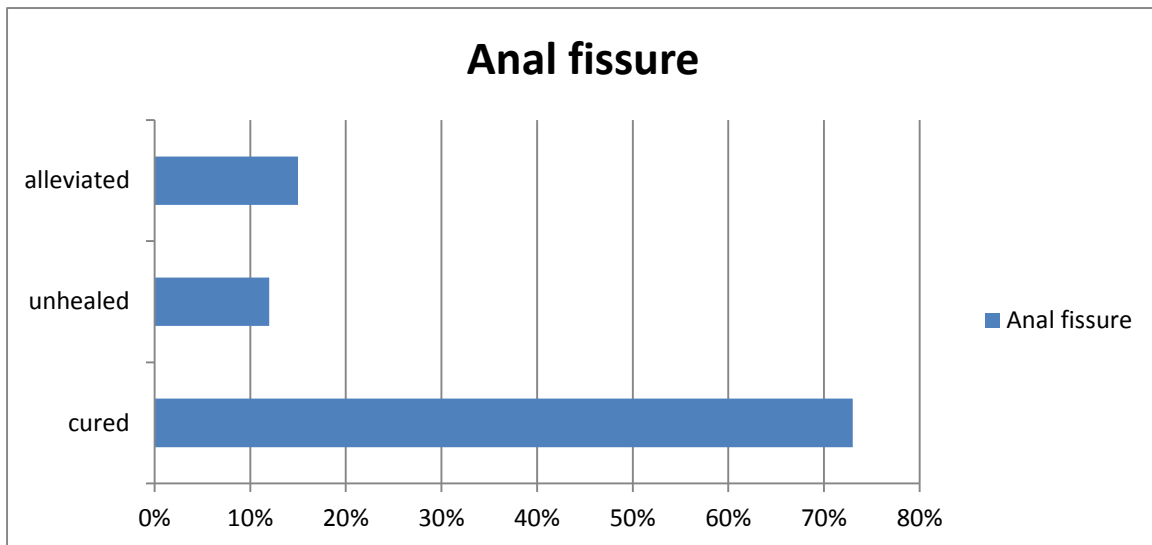


Figure 2. Anal fissure cure rate

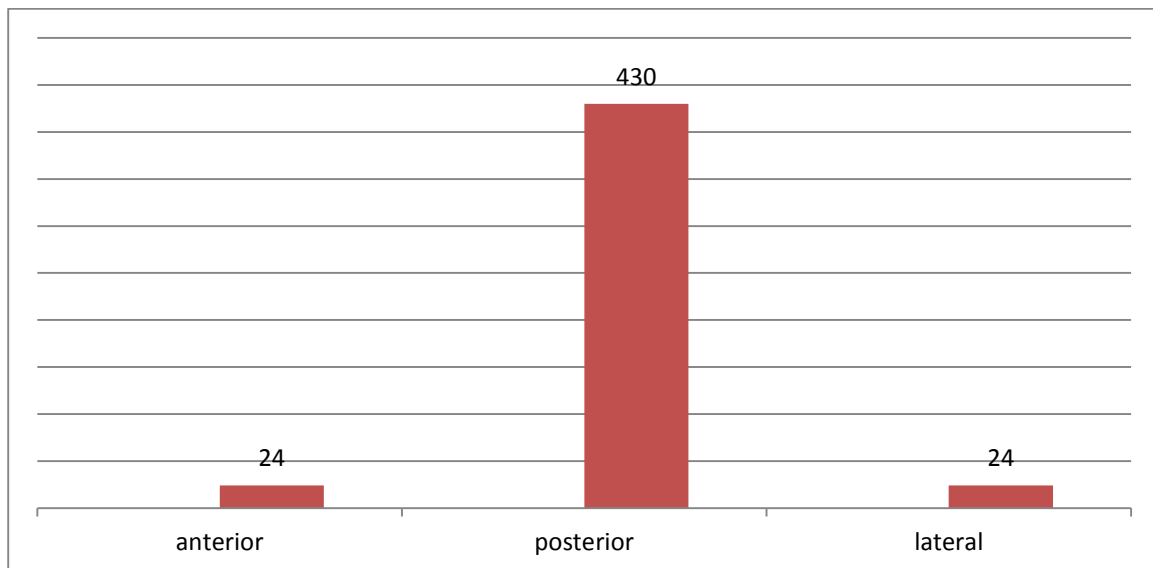


Figure 3. Anal fissure location

## DISCUSSIONS

Acute anal fissures should be treated conservatively by topical ointments, consisting of nitrates, calcium channel blockers and if all else fails by botulinum toxin. Lateral internal sphincterotomy is associated with a certain degree of incontinence and needs mandatory long-term observation. (Heitland W. Et al., 2012)

In a study carried out by Knight, 71 consecutive patients with chronic anal fissure were treated with diltiazem 2% ointment for 9 weeks (Knight JS et al., 2001). About 88% of patients healed with diltiazem ointment. Four patients experienced perianal dermatitis and one patient suffered from headache. After 32 week completion of the treatment, 27 of 41 patients available remained symptom-free. Six of seven patients with

recurrent fissure were treated successfully by repeating diltiazem treatment.

In yet another study, DasGupta's study, patients with chronic anal fissure were treated topically with 2% diltiazem gel three times daily (DasGupta R et al., 2002). Twenty-three patients (12 women) with median age of 45 years had a median 6 months history of fissures. These were associated with a sentinel tag in 39% patients. The fissure healed in 48% of patients, including 75% of patients who previously failed to heal with glyceryl trinitrat ointment. There were no recurrences at 3 months and no adverse effects. (DasGupta R et al., 2002)

Some researchers have compared oral diltiazem with topical diltiazem. A study performed by Jonas assessed the effectiveness of oral and topical diltiazem in healing chronic anal fissure

(Jonas M et al., 2001). Fifty consecutive patients with chronic anal fissure were randomly included in the study. Twenty-four patients received oral (60 mg) and 26 received topical (2% gel) diltiazem twice daily for up to 8 weeks. Anal manometry and blood pressure were recorded at 15-min intervals.

Every 15 days, patients were assessed on the basis of pain alleviation, fissure healing, and side effects. After 8 weeks, fissure healing was complete in 38% and 65% in patients with oral and topical diltiazem treatment by 8 weeks, respectively. Side effects included rashes, headache, nausea, and vomiting, that were observed in eight patients of the oral diltiazem group, whereas no side effects were seen in those receiving topical therapy. Thus topical diltiazem was found to be more effective with no side effects. Carapeti conducted three studies each involving 10 healthy volunteers. In the first study, subjects were given oral diltiazem (60 mg) or placebo on separate occasions. They were then given diltiazem once or twice daily for 4 days. In the second and third studies, diltiazem and bethenachol gels of increasing concentration were applied topically to lower anal pressure (Carapeti EA et al., 1999). Diltiazem gel (2%), bethenachol (0.1%), and oral diltiazem twice daily produced 28%, 24%, and 17% reductions in anal pressure, respectively. In a study reported by Jonas (Jonas M et al., 2002), the efficacy of diltiazem for fissures that failed to heal with glyceryl trinitrat was evaluated. Consecutive patients (N = 39, median age 42 year) with persistent chronic anal fissure despite treatment with glyceryl trinitrat ointment (0.2%) underwent anal manometry before and at 1 h after application of diltiazem gel (700 mg of 2%) to the distal anal canal. The gel was applied twice daily for 8 weeks. Fissure healing and side effects were noted every 15 days.

Topical diltiazem gel lowered maximal anal pressure by 20% and fissures healed in 49% of patients within 8 weeks. Before diltiazem, 69% had used a complete course of glyceryl trinitrat (0.5 g twice daily for 8 weeks), and 44% of patients healed with diltiazem. Some of the patients had discontinued glyceryl trinitrat prematurely because of headaches. Side effects including perianal itching, headache, drowsiness, and mood swings occurred in 10% of patients during diltiazem treatment. Hence, the authors concluded that topical diltiazem (2%) was effective treatment for glyceryl trinitrat-resistant chronic anal fissure.

In a study conducted by Knight et al, fifty-one patients (75 per cent) experienced healing of the fissure after 2-3 months of treatment with topical diltiazem. Seventeen patients who did not heal were treated for further 8 weeks with topical diltiazem. Eight of these patients subsequently healed with diltiazem. Fifty-nine of 67 patients who

completed follow-up therefore healed on diltiazem ointment. Four patients experienced perianal dermatitis and one patient experienced headaches. No other side-effects were recorded. After a median of 32 (range 14-67) weeks follow-up following completion of treatment, 27 of 41 patients available remained symptom free. Six of seven patients with recurrent fissure were treated successfully by repeat chemical sphincterotomy. (Knight JS et al., 2001)

Medhi B found six observational studies with 392 patients and five controlled clinical trials with 289 patients in which topical diltiazem treatment was given. Efficacy was found to be very high in observational studies (56.88%), whereas it was found to be modest in controlled clinical trials (29.41%). In observational studies, most of the patients reported complete healing of fissures within 6-12 weeks, whereas in controlled trials healing was reported within 8 weeks, with tolerable adverse effects of diltiazem. On the basis of the above studies, it can be concluded that topical application of diltiazem is useful in the treatment of chronic anal fissure. (Medhi B et al., 2011)

Griffin (Griffin N et al., 2002) used topical DTZ gels to heal patients with chronic anal fissure that had failed previous treatment with topical glyceryl trinitrat (0.2%). Patients (N = 47) with chronic anal fissure who had previously failed at least one course of topical glyceryl trinitrat were recruited prospectively from a single center. They applied diltiazem (700 mg of 2%) cream to the anal verge twice daily for 8 weeks. Forty-four percent of patients who completed treatment were cured of fissures. Another 42% of patients with persistent fissures were symptomatically improved. Thus surgery could be avoided in 70% of patients.

Unlike studies on the same subject we used 4% topical diltiazem local. Average treatment duration was 8 weeks, during which time the ointment was applied twice a day. Of 478 patients with anal fissures that were presented to our clinic, 73% were healed after 8 weeks of treatment with diltiazem 4%. Symptom relief was observed in 15% of cases. Only 12% of our patients were resistant to treatment in the follow-up period of 18 months. After this period only 19% of patients returned to our clinic for recurrence of symptoms.

## CONCLUSIONS

Until now, lateral internal sphincterotomy has been considered to be the gold standard treatment for anal fissure. In the last decade, lateral internal sphincterotomy has been replaced by smooth muscle relaxation in most cases. This medical option aims to achieve the effectiveness of surgery without side effects by means of a

temporary decrease of anal pressures that allows fissures to heal.

More than 80 clinical studies have been reported in the literature, wherein efficacy of smooth muscle relaxation has been assessed. All of these studies have shown that surgery can be avoided in 33–98% of patients by using smooth muscle relaxation.

Our experience proved that Diltiazem 4% local topic for anal fissure is an efficient treatment with good results on short term follow up.

#### **AUTHOR CONTRIBUTION**

All authors have contributed equally to the present work.

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#### **\*Correspondence**

Carmen Neamtu  
 Str. Gradinarilor Nr.43  
 Arad, Romania  
 Mobile: 0723225793  
 Mail: carmen.neamtu@gmail.com