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L. Ansaloni • A. Bernabè • R. Ghetti • R. Riccardi • R.M. Tranchino • G. Gardini

Oral lacidipine in the treatment of anal fissure

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Abstract The aim of this prospective study was to assess the effectiveness in healing anal fissure (AF) of lacidipine, a calcium channel blocker with a better tolerability in comparison to other calcium antagonists. Twenty-one consecutive patients (16 women, 76.2%) with AF (16 chronic, situated posteriorly in 17 patients (81.0%), anteriorly in 4) with a mean age of 37.1 years (SD, 13.6, range, 20–65) were treated with oral lacidipine (6 mg daily) and warm sitz baths for 28 days, adding only stool softeners for patients with constipation. Blood pressure, pain scores (assessed from 0 to 10 on a visual analogue scale) and fissure healing were monitored at 14 days, 28 days and 2 months. At the 14-day and 28-day follow-ups, the mean systolic and diastolic pressures were not significantly different from pre-treatment levels. Seven patients (33.3%) developed side effects, but only one, who developed dyplopia, withdrew from the study at the 14-day control (non-compliance rate with treatment, 4.8%). Pain scores were significantly reduced after 14 days and continued to show a significant reduction throughout the treatment period. Three fissures (14.3%) healed by 14 days and a total of 19 (90.4%) after 28 days: among the healed AF no recurrences were seen at the 2-month control. Among the two treatment failures, one was the patient who withdrew from the study at the 14-day control due to dyplopia and the other was a patient who failed to heal up to the 2-month follow-up, although completely asymptomatic. Both patients underwent left lateral sphincterotomy and healed. In conclusion, oral lacedipine is quite well tolerated and may offer a promising alternative treatment for AF.

Key words Fissure in ano • Calcium channel blockers

L. Ansaloni (✉)
Department of Emergency Surgery
S. Orsola-Malpighi Hospital
Via Massarenti 9
I-40138 Bologna, Italy
e-mail: so10790@iperbole.bologna.it

A. Bernabè • R. Ghetti • G. Gardini
Department of General Surgery
Lugo Hospital
Ravenna, Italy

R. Riccardi • R.M. Tranchino
Department of General Surgery
Faenza Hospital
Ravenna, Italy

Introduction

Anal fissures (AF) are thought to arise as a consequence of hypertonia of the internal anal sphincter (IAS), which impedes blood flow to the anal mucosa [1]. It is well demonstrated that in about 70%–80% of cases, AF are localised to the posterior anal commissure [2, 3] where the anoderm is less well perfused than other segments of the anal canal [4, 5] and its perfusion is strongly related to the anal pressure [6]. AF are therefore considered to be ischaemic ulcers of the anal canal, due to the increased activity of the IAS; therefore the reduction of IAS tone is the most important step in the treatment of AF [7, 8].

As calcium ions play an important role in muscle contraction, calcium channel blockers, such as nifedipine and diltiazem, that inhibit smooth muscle excitation produced an abolition of resting tone in IAS smooth muscle in vitro [9, 10] and reduced resting anal pressure. Thus calcium channel blockers can heal AF, although with a high rate of side effects [11–15]. The aim of this study was to assess the effectiveness of lacidipine, a calcium channel blocker with a better tolerability in comparison to nifedipine and other calcium antagonists [16, 17], in healing AF.

Patients and methods

Outpatients with AF seen in Lugo and Faenza Hospitals, Ravenna, Italy, under the care of two colorectal units between September 2000 and May 2001 were studied prospectively. Patients with Crohn's disease were excluded. AF was considered to be present if the patient presented with a history of anal pain on defecation and the examination typically revealed a fissure. The AF was defined chronic, when pain lasted for more than 2 months and the fissure showed features of chronicity, such as exposure of the internal anal sphincter, induration of the fissure edges, development of a large sentinel pile and hypertrophied anal papilla.

A total of 21 consecutive patients (16 women, 76.2%) with AF (16 chronic) with a mean age of 37.1 years (SD, 13.6; range, 20–65) were treated with oral lacidipine (6 mg daily) and warm sitz baths [18] for 28 days. Stool softeners were given to patients with constipation. Although patients were not prescribed topical analgesic creams for the duration of treatment, a high-fiber diet was encouraged. AF was situated posteriorly in 17 patients (81.0%), anteriorly in 4. For 20 patients (95.2%) it was the first episode of AF (for the remaining one, the second recurrence) and 9 patients (42.9%) had already used other conservative treatments (topical anaesthetic creams and stool softeners) without improvement. In 5 patients (23.8%), haemorrhoids were present. Blood pressure, pain scores (assessed from 0 to 10 on a visual analogue scale (VAS) ranging from "no pain" to "worst pain imaginable") and fissure healing were monitored at 14 days, 28 days and 2 months. Healing was defined by resolution of symptoms (anal pain and bleeding) and the absence of a fissure on examination.

The statistical analysis was carried out using Epi Info, Version 6.02 software package (CDC, Atlanta, Georgia, USA, 1994). The Kruskal-Wallis H test was used to compare mean pre- and post-treatment values.

Results

At the 14-day and 28-day follow-up, the mean systolic and diastolic blood pressures were not significantly different from pretreatment levels (Table 1). Seven patients (33.3%) developed side effects (headache in 2 patients, palpitations in 2, flushing, dizziness, colic abdominal pain, ankle oedema and dyplopia in one each). Only the patient who developed dyplopia withdrew from the study at the 14-day control (non-compliance rate with treatment 4.8%).

Pain scores were significantly reduced after 14 days and continued to show a significant reduction throughout the treatment period (Table 2). Three fissures (14.3%) healed by 14 days and a total of 19 (90.4%) after 28 days: among the AF healed no recurrences were seen at the 2-month control. There were two treatment failures: the first patient withdrew from the study at the 14-day control due to a side effect of the drug treatment (dyplopia) and the other was a patient in whom the fissure failed to heal up at the 2-month follow-up. In the first case the VAS was 8 before the treatment and 1 at the 14-day control; in the second the VAS was 0 at the 2-month follow-up. Both patients underwent surgical left lateral sphincterotomy, because the fissure was still present, and both of them healed completely.

Table 1 Mean systolic and diastolic blood pressures at the 14-day and 28-day follow-ups. Values are mean (SD)

	Systolic pressure		Diastolic pressure	
Before treatment	121.9	(8.7)	77.1	(10.5)
14-day follow-up	120.5	(8.0)	71.9	(9.3)
28-day follow-up	118.5	(3.4)	71.5	(8.7)

Table 2 Pain scores at the 14-day, 28-day and 2-month follow-ups. Values are mean (SD)

	Pain score	
Before treatment	6.8	(1.6)
14 days	0.8	(1.0)*
28 days	0	(0)
2 months	0	(0)

*$p<0.000001$ vs. pretreatment values (Kruskal-Wallis H test)

Discussion

As both clinical and manometric findings indicate an association of AF with sustained hypertone of IAS [19], the treatment is aimed at decreasing high sphincter pressure. Surgery has been the traditional and accepted treatment [20, 21], but all the operative techniques commonly used for AF, including anal stretch, posterior and lateral sphincterotomies, show obvious disadvantages, such as hospitalization and anesthetic and surgery risks, and may result in an irreparable damage to IAS. Therefore in the long-term outcome of all surgical procedures, a variable but consistent percentage of patients experiences some form of incontinence [22–27]. This significant complication and the improved knowledge of the neurophysiology of the IAS [28, 29] has led to a search for alternative treatments for AF. Attempts have been made at reversible reduction of anal pressure and some of them are effective, like insertion of anal dilators [30], local injection of botulinum toxin [31], and "chemical sphincterotomy" with a pharmacologic approach [32]. In the latter attempt two categories of drugs have been used on clinical grounds to reduce the IAS tone: nitric oxide donors and calcium antagonists [29]. Local application of exogenous nitric oxide donors, such as isosorbide dinitrate [33] and glyceryl trinitrate [34], has been shown to be effective in the management of anal fissure, but with an high incidence of side effects, especially headache [35]. Some patients experience tachyphylaxis, whereby increasing concentration of paste are required to maintain an effect [36].

Concerning calcium antagonists, in 1987 it was showed that anal resting pressure decreased shortly after oral administration of 60 mg diltiazem; based on this finding, treatment with this calcium channel blocker was advocated in patients with proctalgia fugax [37]. More recently, two calcium channel blockers, nifedipine and diltiazem, have been used topically with a good rate of AF healing [12–15, 38]. In topical treatments, there may be confusion as to whether paste should be applied around the anal margin or within the anal canal, and the volume of paste that should be applied is also unclear. As an oral preparation could overcome some of the potential confusion with site of application and dose, Cook and colleagues showed that oral administration of 20 mg nifedipine twice daily reduced resting anal pressure and healed AF [11], although with a high side effect rate [39].

Unlike most of the other calcium antagonists, including nifedipine, that have a relatively short duration of action and need to be administered 2–3 times daily, lacidipine is a calcium antagonist with a long duration of action, allowing a once-daily administration [40]. Moreover lacidipine is better tolerated in comparison to nifedipine and other calcium antagonists [16, 17]. Our study has demonstrated that lacidipine, given orally in single daily dosage of 6 mg, with a healing rate of 90% at the 28-day follow-up, may be used successfully to treat AF. The significant reduction in pain scores within the first two weeks of treatment (which continued throughout the period of study) and the alleviation of symptoms in the only patient in whom the AF failed to heal provide further support for a role for lacidipine in the treatment of AF. Follow-up measurements of systolic and diastolic blood pressure were not significantly different from pretreatment levels and only 33% of patients experienced side effects. We conclude that, although further prospective randomized controlled trials with long-term follow-ups are needed, oral lacidipine is quite well tolerated and offers a promising alternative treatment for AF.

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Invited comment

This is one of several papers dealing with medical treatment of anal fissure by "chemically induced sphincterotomy" that have appeared in surgical journals in the last 3–4 years. A new selective calcium channel blockers has been tested after oral instead of topical administration. The paper, however, belongs to the lowest category of quality of scientific evidence as listed by the British Medical Council as there are no controls and the treatment was not randomised to minimize any bias in the study. To demonstrate a cause-effect of lacipidine on anal tone and then on the fissure healing, anal manometric data cannot be set aside like in this paper. On the other hand, the authors could not document any effect of this drug on blood pressure using the dosages reported. One could argue that even the anal resting tone did not change in these patients. In that case why should the fissures heal? Finally the follow-up period, which is the true Achille's heel of these papers, is indeed very short and insufficient to exclude any recurrence of the fissure. The Authors are encouraged to continue this interesting and thought provoking study in a larger series with longer follow-up.

D.F. Altomare
University of Bari,
Bari, Italy