Topical Nifedipine With Lidocaine Ointment vs. Active Control for Treatment of Chronic Anal Fissure

Results of a Prospective, Randomized, Double-Blind Study

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PURPOSE: Chronic anal fissure may be treated by chemical or surgical sphincterotomy. The aim of this study was to test the efficacy of local application of nifedipine and lidocaine ointment in healing chronic anal fissure. METHODS: The study was performed according to a prospective, randomized, double-blind design. One hundred ten patients who gave informed consent were recruited. They received a clinical examination, a questionnaire to evaluate symptoms and pain, anorectal manometry, and anoscopy. Healing of anal fissure at Day 42 of therapy was defined as the primary efficacy variable of the study. Patients treated with nifedipine (n = 55) used topical 0.3 percent nifedipine and 1.5 percent lidocaine ointment every 12 hours for 6 weeks. The control group (n = 55) received topical 1.5 percent lidocaine and 1 percent hydrocortisone acetate ointment during therapy. Anal pressures were measured by recording resting and maximal voluntary contraction pressures at baseline and at Day 21. Long-term outcomes were determined after a median follow-up of 18 months. RESULTS: Healing of chronic anal fissure was achieved after 6 weeks of therapy in 94.5 percent of the nifedipine-treated patients (P < 0.001) as opposed to 16.4 percent of the controls. Mean anal resting pressure decreased from a mean value ± standard deviation of 47.2 ± 14.6 to 42 ± 12.4 mmHg in the nifedipine group. This represents a mean reduction of 11 percent (P = 0.002). Changes of maximal voluntary contraction in nifedipine-treated patients were not significant. No changes in mean anal resting pressure and maximal voluntary contraction were observed in the control group. We did not observe any systemic side effect in patients treated with nifedipine. After the blinding was removed, recurrence of the fissure was observed in 3 of 52 patients in the nifedipine group within 1 year of treatment, and 2 of these patients healed with an additional course of topical nifedipine and lidocaine ointment. CONCLUSIONS: Our study clearly demonstrates that the therapeutic use of topical nifedipine and lidocaine ointment should be extended to the conservative treatment of chronic anal fissure. [Key words: Anal fissure; Treatment; Chemical sphincterotomy; Nifedipine]


Pathologies of the anal canal (acute and chronic fissures and hemorrhoids) are extremely common. A fissure is an oval, ulcer-like lesion in the anoderm, distal to the dentate line. Acute anal fissures are superficial splits; they cause acute stabbing and burning pains in the anal canal during and after defecation, and most heal spontaneously. Chronic anal fissures are associated with hypertonia of the anal canal and a reduction in mucosal blood flow, with microcirculatory disturbance and a poor healing tendency. Surgery has been the traditional treatment for chronic anal fissure. Reduction of anal pressure by sphincterotomy or by anal dilation improves anodermal blood flow at the posterior midline, resulting in fissure healing. However, the postoperative period may be marked by surgical risks, complications, and a late incidence of incontinence that is sometimes permanent. Recently, new pharmacologic therapies have been used to create a reversible chemical reduction of sphincter pressure until the fissure has healed. Several studies showed healing of anal fissure with a variety of novel agents, including botulinum toxin, isosorbide dinitrate and glyceryl trinitrate, and calcium channel blockers, such as diltiazem or nifedipine. Initial promising results of topical glyceryl trinitrate were impaired because of poor outcomes and side effects. Moreover, transitory fecal incontinence, side effects, and recurrence were reported after local infiltration of botulinum toxin. Topical diltiazem ointment has been shown to be effective, but some patients experienced perianal dermatitis and headaches. Nifedipine, a dihydropyridine,
is a calcium antagonist that is presently only administered orally for cardiovascular disorders and that causes smooth muscle relaxation and vasodilation. Topical preparations of nifedipine have recently been shown to lower anal resting pressure, relieve pain, and heal acute anal fissures and acute thrombosed hemorrhoids. The aim of the present study was to test the efficacy of a new preparation of nifedipine and lidocaine ointment in the treatment of chronic anal fissure and to compare the investigational product with an active control, according to a prospective, randomized, double-blind design.

PATIENTS AND METHODS

Patients

Consecutive patients (n = 110) were recruited from April to December 1999. The study was performed at the Emergency Surgery and the Gastroenterology Department of the A. Cardarelli Hospital in Naples, Italy.

Inclusion criteria were males and females 18 years and older with chronic anal fissure. Chronic anal fissure was defined at clinical examination when induration at the edges was visible and horizontal fibers of the internal anal sphincter could be seen in the base of the lesion. A history of anal pain on defecation for at least two months that had failed to resolve with stool softeners and simple topical anesthetic agents was required to be present.

Exclusion criteria were 1) presumed or confirmed pregnancy, 2) allergy to nifedipine or lidocaine, and 3) associated complications warranting surgery (abscess, fistula, and cancer). Concomitant first-degree to third-degree hemorrhoids were not considered an exclusion criteria.

Study Design

A prospective, randomized, double-blind study with active treatment control was performed. Written informed consent was given by each participant. In conformity with the Good Clinical Practice guidelines, the study was approved by the ethics committee of the A. Cardarelli Hospital in Naples, Italy. This clinical trial was regarded as a Phase 3 level of clinical study of a new pharmacologic preparation of nifedipine and lidocaine ointment (New Fa.Dem, Chemicals and Pharmaceuticals, s.r.l., Gingliano, Italy) before application to request approval for marketing from the Italian Ministry of Health.

The aim of the study was to test the efficacy of local application of nifedipine and lidocaine ointment in healing chronic anal fissure by reducing mean anal resting pressure and relieving patients of pain. Objective changes were assessed by clinical examination at every consultation by an observer blinded to the treatment arm at baseline and on Days 21 and 42. Anoscopy was performed at baseline and on Day 42. Healing of chronic anal fissure was used as the primary efficacy variable of the study, and it was defined at anoscopy when epithelialization or formation of a scar was achieved at Day 42 of therapy.

Secondary variables of efficacy were defined as conditions that might facilitate the healing process by reducing mean anal resting pressure, a function of internal anal sphincter activity, and by relieving anal pain. These conditions were stated at baseline and at Day 21. Subjective changes were assessed by a questionnaire to evaluate pain and symptoms. Pulse and blood pressure, any side effects, and pain scores were recorded at each visit. Anal pain was classified on a linear analog pain score (range, 0–10) as persistent (range, 8–10), modest (range, 4–7) or absent (range, 0–3).

Manometric studies were used to demonstrate objective changes in anal pressures. They were performed at baseline and on Day 21, and manometry pressure traces were examined by an investigator blinded as to the preparation administered. A 4.7-mm-diameter polyvinyl chloride catheter with 4 side holes oriented at 45° to one another (DRWG/C7-R8–0010, Mui Scientific, Mississauga, Ontario, Canada) was used. The catheter was continuously perfused with a pneumohydraulic pump (Dyno® Compact, Menfis bioMedica s.r.l., Bologna, Italy); the infusion rate was 0.5 ml per channel per minute. Recordings and analyses of the tracings were made by a computerized system (Dyno® Software, Menfis bioMedica s.r.l.). Anal resting pressure was recorded in millimeters of mercury with the stationary pull-through technique, and the computer identified the mean pressure. The maximal voluntary contraction was examined by evaluation of the voluntary contractions of anal sphincter. Amplitude was expressed in millimeters of mercury.

The 110 consecutive patients who satisfied the selection criteria were divided into 2 groups at the initial consultation according to a computer-generated centralized randomization list kept in the pharmacy department. The control group received local application of an ointment containing 1.5 percent lidocaine and 1 percent hydrocortisone acetate, whereas the