Clinical Science

Randomized controlled pilot trial of nifedipine as oral therapy vs topical application in the treatment of fissure-in-ano

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Fissure-in-ano; Anal fissure; Nifedipine; Treatment

Abstract

BACKGROUND: Fissure-in-ano is a common condition that leads to pain and affects quality of life. Sphincterotomy remains the gold standard, but it may lead to troublesome incontinence in some patients. To overcome this problem, numerous pharmacologic therapies have been tested with varying outcomes. The investigators compared the effect of the addition of oral and topical nifedipine to conservative measures in the treatment of patients with fissure-in-ano.

METHODS: Ninety patients with fissure-in-ano, randomized into 3 groups of 30 each, were included in the study. Group I received conventional treatment, group II received oral nifedipine and conventional treatment, and group III received topical nifedipine along with conventional treatment. Patients were followed for 8 weeks for pain relief (assessed using a visual analogue scale) and healing to evaluate the effect of treatment.

RESULTS: Pain relief was significantly better in the group III at 3 weeks and 2 months compared with group I (P < .05). Groups II and III were comparable in terms of pain relief. Healing rates were significantly better in group II (P = .03) and group III (P = .00) compared with group I, but groups II and III were found to be comparable. Adverse effects were most commonly reported by group II patients, but these were not significantly higher than in other 2 groups.

CONCLUSIONS: We recommend the addition of either oral or topical nifedipine to conservative measures to significantly improve pain relief and healing rates in patients with fissure-in-ano.
cases.8–12 This has lead to a search for alternative means of management to minimize the incidence of incontinence secondary to permanent sphincter injury.

Chemical sphincterotomy is aimed at reducing mean resting anal pressure without inducing permanent sphincter injury.13,14 Many preparations have been used, including nitrates, adrenergic antagonists, topical muscarinic agonists such as bethanechol, phosphodiesterase inhibitors, botulinum toxin, and oral and topical calcium channel blockers including nifedipine and diltiazem.

There is an ongoing debate over the benefit of one preparation over the other as well the method of use of various preparations. The availability of a large number of drugs suggests that we are yet to establish the superiority of any particular drug as the preferred agent for fissure management. The aim of this study was to take a step forward in this direction by comparing the relative efficacy of topical and oral nifedipine in the treatment of patients with fissure-in-ano.

Methods

Patients

Consecutive patients aged 18 to 50 years presenting to the surgery outpatient department with painful bleeding per rectum and confirmed to have fissure-in-ano on clinical examination were studied. Informed consent was obtained from each patient. Patients with complicated fissures (fissures at atypical locations associated with tuberculosis or Crohn’s disease), fissures coexisting with systemic diseases (diabetes, human immunodeficiency virus infection, and other immune-compromised states), patients allergic to calcium channel blockers, and pregnant and lactating women were excluded.

Study design

The study was an open-label, randomized controlled pilot trial. It was conducted in a single surgical unit of a tertiary care hospital in New Delhi, India, as a part of research work for a postgraduate degree in surgery. The study was conducted over a period of 1 year commencing in January 2010. Clearance was obtained from the institutional ethics committee. A total of 90 patients were included, randomized into 3 groups comprising of 30 patients each, according to a computer-generated table of random numbers.

Group I included patients who received conservative treatment in the form of fiber supplementation (psyllium husk 2 tsp at bedtime), stool softener (lactulose syrup 15 mL at bedtime), lignocaine ointment for local application before the act of defecation, warm sitz bath twice daily for 30 minutes each, and oral antibiotics (doxycycline 100 mg/day and metronidazole 400 mg thrice daily) for 5 days. Patients in group II, in addition to conservative treatment, received oral nifedipine in the form of 20-mg controlled-release tablets twice daily. Patients in group III were given nifedipine ointment 0.2% for local application into the anal canal twice daily along with conservative treatment. The ointment was freshly prepared in the Department of Pharmacology of the University College of Medical Sciences and Guru Teg Bahadur Hospital and dispensed weekly in dark containers. Patients were instructed to self-apply an almond-sized amount of ointment into the distal anal canal after a sitz bath.

Calcium channel blockers inhibit \( \text{Ca}^{2+} \) influx through voltage-sensitive \( L \)-type calcium channels in smooth muscles, thus leading to smooth muscle relaxation and enhanced blood flow. Calcium channel blockers inhibit \( \text{Ca}^{2+} \) influx through voltage-sensitive \( L \)-type calcium channels in smooth muscles, thus leading to smooth muscle relaxation and enhanced blood flow.15 These drugs act against the basic pathophysiology behind this disease and thereby promote healing.

Healing of fissure-in-ano as evident by complete epithelialization of fissure-bearing area on clinical examination was taken as the primary outcome, while improvement in pain scores on a visual analogue scale (VAS) was the secondary outcome of our study. Patients were prospectively followed; intragroup and intergroup comparisons were made at 1 week, 3 weeks, and 2 months for improvement in pain scores, while assessment of healing was made at the end of 2 months.

Statistical analysis

Results were analyzed using SPSS version 17.0 (SPSS, Inc, Chicago, IL). Pain scores were compared using repeated-measures analysis of variance, while healing rates among the 3 study groups were compared using Fischer’s exact test. \( P \) values <.05 were considered significant.

Results

Patients in all 3 groups were found to be comparable with respect to age, gender composition, duration of symptoms, and severity of pain at the time of inclusion in the study (Table 1).

There were significant improvements in VAS scores in each of the 3 groups by the end of 3 weeks of treatment, and pain relief was sustained throughout our follow-up period of 2 months (Fig. 1). Pain relief was quicker and significantly better in patients treated with topical nifedipine compared with conservative treatment alone (\( P < .05 \)). Pain relief was apparently better in group II than in group I, but the difference was not statistically significant (\( P > .05 \)). Topical and oral applications of nifedipine were comparable in terms of providing relief of pain in patients with fissure-in-ano.

Healing in the conservative treatment group (14 of 30 [47.67%]) was significantly lower than in the groups that received topical nifedipine (27 of 30 [90%]) and oral nifedipine (23 of 30 [76.33%]) (\( P = .00 \) and \( P = .03 \), respectively).
respectively; Fig. 2). On comparing oral nifedipine with topical nifedipine, higher healing rates were observed in patients who received the topical preparation, but the results were not statistically significant ($P = .29$).

The highest incidence of side effects was reported by patients in group II (4 of 30), but this was not significantly higher than the incidence of side effects observed in group III (1 of 30). Headache was the most common side effect, it was seen in 3 of 30 patients in group II and 1 patient in group III. One patient treated with oral nifedipine reported ankle edema.

**Comments**

The intergroup comparison of VAS scores for pain (Fig. 1) revealed comparable results for conservative treatment compared with oral nifedipine and for oral nifedipine compared with topical nifedipine at all points in time. Significant differences in pain scores were noted between groups I and III at 3 weeks and 2 months ($P < .05$). This shows that addition of topical nifedipine to conservative treatment helps provide rapid pain relief and makes treatment more efficacious in patients with fissure-in-ano. The efficacy of topical nifedipine in providing pain relief was also investigated by Ezri and Susmallian, who reported a significant improvement in pain, measured using VAS scores, which reduced from 6.1 to 3.4 in their study.

In the oral nifedipine group, although the rate and extent of improvement in pain scores were better than those observed with conservative treatment alone, the difference was not statistically significant ($P > .05$). Similar efficacy of oral nifedipine was highlighted in study conducted by Mustafa et al., who reported a significant improvement in pain scores with oral dosing (20 mg twice daily) of nifedipine after 2 weeks of treatment. In our study, groups II and III were found to be comparable in pain relief at all similar points of time ($P > .05$; Fig. 1).

Healing was significantly better with topical nifedipine (90%) and oral nifedipine (76.33%) compared with conservative treatment alone (46.67%; Fig. 2), while topical and oral nifedipine were comparable in promoting healing. Various authors have reported similar healing rates with topical nifedipine. Antropoli et al. in their randomized trial used 0.2% nifedipine gel for local application and compared it with topical application of lignocaine and hydrocortisone; they reported 95% healing in the nifedipine group after 3 weeks. Perrotti et al. used 0.3% nifedipine gel and reported a healing rate of 94.5%. A similar healing rate of 89% was reported by Ezri and Susmallian using 0.2% topical nifedipine. Our results with oral nifedipine also concur well with the results published by other authors. Cook et al. used oral nifedipine 20 mg twice daily and observed relief of symptoms in 80% of patients and healing in 60% of patients after 8 weeks. Healing rates of 60% were reported in 2 other studies after twice-daily oral dosing (20 mg) of nifedipine in the treatment of patients with fissure-in-ano. Diltiazem offers healing rates of 49% to 89.4%, as reported by various authors. Healing rates reported with nitroglycerine range from 46% to 68%. Diltiazem offers healing rates of 49% to 89.4%, as reported by various authors.

In our study, the maximum occurrence of side effects was noticed in the group taking oral nifedipine. Comparable results were reported in a study conducted by Mustafa

### Table 1 Comparison of baseline parameters in each group

<table>
<thead>
<tr>
<th>Variable</th>
<th>Group I (n = 30)</th>
<th>Group II (n = 30)</th>
<th>Group III (n = 30)</th>
<th>$P$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (y)</td>
<td>31.23 ± 10.04</td>
<td>32.50 ± 9.43</td>
<td>32.40 ± 9.13</td>
<td>.850</td>
</tr>
<tr>
<td>Male/Female</td>
<td>19/11</td>
<td>17/13</td>
<td>19/11</td>
<td>&gt;.05</td>
</tr>
<tr>
<td>Duration of symptoms (d)</td>
<td>30 (3–180)</td>
<td>45 (4–240)</td>
<td>30 (4–180)</td>
<td>.323</td>
</tr>
<tr>
<td>Pain score (VAS)</td>
<td>8.07 ± 1.95</td>
<td>8.27 ± 1.70</td>
<td>8.17 ± 1.74</td>
<td>.912</td>
</tr>
<tr>
<td>Constipation</td>
<td>29 (96.67%)</td>
<td>26 (86.67%)</td>
<td>23 (76.67%)</td>
<td>&gt;.05</td>
</tr>
<tr>
<td>Bleeding</td>
<td>18 (60%)</td>
<td>20 (66.67%)</td>
<td>21 (70%)</td>
<td>&gt;.05</td>
</tr>
</tbody>
</table>

Data are expressed as mean ± SD, number (percentage), or median (range).
et al., in which the authors reported a 10% incidence of side effects with oral nifedipine. None of the patients reported flushing or postural hypotension. In group III (receiving topical nifedipine), only 1 patient (3%) reported the occurrence of headache. Our results concur well with the study conducted by Ezri and Susmallian, who reported a 5% incidence of side effects in patients treated with topical nifedipine.

Conclusions

The addition of either oral or topical nifedipine to conservative measures significantly improves healing rates in the treatment of patients with fissure-in-ano. It helps in achieving a higher degree of pain relief more quickly. Both topical and oral preparations of nifedipine are comparable in terms of efficacy and side effects.

We recommend that oral nifedipine be used as a first-line drug in the treatment of fissure-in-ano for ease of compliance, as oral therapy is simpler to follow and produces healing comparable with that produced by topical nifedipine. If 0.2% nifedipine could be produced commercially, another effective ointment would be available for the treatment of patients with fissure-in-ano.

References