Randomized, double-blind trial comparing topical nitroglycerine with xylocaine and *Proctosedyl* in idiopathic chronic anal fissure

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Objective: To compare symptomatic relief, healing, and changes in maximal anal resting pressure with the use of topical formulations in patients with chronic anal fissure. Methods: Sixty-four consecutive patients with chronic anal fissure were randomized into 4 groups that received, in a double-blind manner, a topical ointment that contained 0.2% nitroglycerine (GTN), 5% xylocaine, *Proctosedyl* (hydrocortisone acetate, heparin, framycetin sulfate, esculose, ethosulfate, butyrospermum or petroleum jelly (Vaseline), to be applied twice daily. Patients were reviewed at 2-week intervals for 6 weeks. Anal manometry was done before, and 20 minutes after, the first application of the ointment. Results: There was significant (p<0.0001) reduction in mean anal resting pressure after application of GTN, but not any other ointment. Of 16 patients receiving GTN, complete pain relief occurred in 6 and 15 patients after 2 and 4 weeks of treatment, respectively; this was more frequent than in the other 3 groups. At 6 weeks also, complete pain relief occurred more often with GTN than with Vaseline or xylocaine. After 4 weeks of treatment, 3 patients on GTN had complete healing of fissure as compared to one each in the xylocaine and *Proctosedyl* groups and none in the Vaseline group. At 6 weeks, healing of fissure had occurred in 15 of 16 patients receiving GTN as compared to 4 receiving Vaseline, 11 receiving xylocaine, and 12 on *Proctosedyl*. Conclusions: Topical nitroglycerine produces 'chemical sphincterotomy' with reduction in mean anal resting pressure. Pain relief and healing of fissure occurred earlier with GTN than with other treatments. GTN should be considered as the treatment of choice for the non-surgical management of patients with chronic anal fissure.

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Key words: Fissure-in-ano, lidocaine

Chronic anal fissures usually do not heal without intervention. Chronicity of anal fissures is related primarily to overactivity and hypertonia of the internal anal sphincter muscle. Presently, surgical methods like internal sphincterotomy or anal dilatation are the treatment of choice to overcome sphincteric hypertonia. Both these methods are however associated with disturbance of fecal continence in a sizeable proportion of patients. Nitric oxide has recently been shown to be an important neurotransmitter in nerve-mediated relaxation of the internal sphincter. Topical application of nitrates, which provide nitric oxide, in low concentration has shown promising results in patients with acute and chronic anal fissures.

We compared symptom relief, ulcer healing and changes in maximal anal resting pressures (MAP) with the use of topical nitroglycerine (GTN), xylocaine, petroleum jelly or a proprietary formulation (*Proctosedyl*) in patients with chronic anal fissure.

Methods

Sixty-four consecutive consenting patients with chronic anal fissure were included in the study after approval of the protocol by the institutional ethics committee. Chronicity was defined as symptoms (pain, bleeding) lasting more than one month, induration of the fissure, fibers of sphincter muscle visible at base of fissure, and sentinel pile. Patients with secondary fissures, systemic diseases (diabetes mellitus, jaundice, collagen diseases), pregnancy, or those on treatment with nitrates for other diseases were excluded.

The patients were randomized into four treatment groups of 16 patients each using a 4x4 Latin square design with column-to-column and row-to-row randomization technique (i=4). The control variables were age and weight in four groups, viz., A1 A2 A3 A4 and W1 W2 W3 W4, respectively. Two replicates were taken for each gender independently with each replicate having 16 patients (4 in each group). This ensured that the groups were comparable for age, sex and weight.

The four groups were allocated to different treatments. Group A received petroleum jelly (Vaseline; Hindustan Lever, Pondicherry), Group B received xylocaine 5% (Lignocaine; Astra-IDL), Group C received a proprietary ointment (*Proctosedyl*: Hoechst Marion Roussel, Goa; contains hydrocortisone acetate, heparin, framycetin sulfate, esculose, ethosulfate, butyrospermum, and Group D received GTN ointment (Myovin; Cadila Pharma; contains 2% nitroglycerine, made to 0.2% with petroleum jelly in our Department of Pharmacology) for topical application. All preparations were dispensed in identical wide-mouthed plastic jars for application with a finger-
Table 1: Demographic features of treatment groups

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Vasoline (n=16)</th>
<th>Xylocaine (n=16)</th>
<th>Proctosedyl (n=16)</th>
<th>Nitroglycerine (n=16)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>31 (21-39)</td>
<td>32 (21-40)</td>
<td>32 (22-39)</td>
<td>34 (21-35)</td>
</tr>
<tr>
<td>Male:female</td>
<td>8:8</td>
<td>8:8</td>
<td>8:8</td>
<td>8:8</td>
</tr>
<tr>
<td>Weight (Kg)</td>
<td>54 (40-72)</td>
<td>56 (39-75)</td>
<td>55 (41-71)</td>
<td>55 (41-72)</td>
</tr>
<tr>
<td>Duration of symptoms (mo)</td>
<td>8 (4-13)</td>
<td>10 (5-14.5)</td>
<td>8.5 (3-15)</td>
<td>9 (4.5-13)</td>
</tr>
<tr>
<td>All values as mean (range)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

The patients were asked to apply about 0.5 g of ointment to the distal anal canal twice daily. They were followed up at 2-week intervals for 6 weeks for relief of pain, healing of fissure, and side-effects of drugs. All patients received supportive measures such as sitz baths and fiber preparations. Pain relief was defined as complete absence of pain; healing of fissure was defined as completely healed fissure with full epithelization.

Anal manometry was done using water-perfused probes with remote sensors (Griffon; Albyn Medical, Scotland) and a station pull-out technique. Average MARP was recorded before, and 20 minutes after, the first application of ointment.

Intergroup comparisons of continuous variables were done using ANOVA followed by contrast t tests (paired or unpaired, as appropriate); for qualitative variables, the chi-squared test was used.

Results

The four treatment groups were comparable in weight, sex and age distribution (Table 1). There were no dropouts. Mean MARP before application of ointment was comparable in the four treatment groups. There was significant reduction in MARP after application of GTN but not of other ointment preparations (Table 2).

After two weeks of treatment, 6 of 16 (38%) patients on GTN had complete pain relief, as compared to none in the other three groups (p=0.0032; Table 3). The number of patients who had pain relief was higher in the GTN group than in the other three groups at 4 and 6 weeks also (p<0.0001 versus jelly).

No patient in any of the groups had healing of the fissure after two weeks of treatment (Table 3). At four weeks, more patients in the GTN group had healing than those on jelly (p=0.0344). At six weeks, healing occurred more often in patients receiving GTN than those receiving jelly (p<0.0001) or xylocaine (p=0.035).

Four patients experienced mild local burning and three had headache with GTN in the first two weeks, which subsided with continued treatment. Three patients on Proctosedyl and one on xylocaine had pruritus ani. No side effects were seen with jelly application.

Discussion

Various studies have found MARP to be higher in patients with anal fissure than in healthy controls. Maximum voluntary squeeze pressure in these patients is similar to that in controls, suggesting that the high MARP is due to hypertoncity of the internal anal sphincter. Also, in patients who respond to conservative treatment, MARP remains high, suggesting that the hypertoncity is not secondary to local pain. An abnormal anorectal inhibitory reflex and a longer high pressure zone has been noted; these findings are however not consistent. Ultra-slow pressure wave activity occurs more frequently in those with chronic anal fissure than in controls. This is abolished after sphincterotomy.

In the treatment of anal fissure, stool softeners, warm sitz baths, local anesthetic agents, steroid-containing ointments, and proteolytic enzyme preparations have been used in various combinations. In a general practitioner study evaluating the efficacy of Proctosedyl ointment, 80.4% of patients had healing after 3 weeks of treatment. Side effects were not assessed in this study.

No published studies are available on the effect of Proctosedyl on resting anal tone.

Sphincterotomy, presently the treatment of choice for chronic anal fissure, lowers resting anal pressure by as much as 26%-50%. High rates of soiling of underclothes has been reported after the procedure.

Anal dilatation is particularly attractive because of its extreme simplicity; however, this technique is difficult to standardize, produces an uncontrolled tear of the sphincter, and is associated with several complications.

Table 2: Mean maximal anal resting pressure before and after treatment

<table>
<thead>
<tr>
<th>Treatment group</th>
<th>Mean maximal anal resting pressure (cmH2O)</th>
<th>Before treatment</th>
<th>After treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vaseline</td>
<td>80.3 (21.6)</td>
<td>79.3 (22.3)</td>
<td></td>
</tr>
<tr>
<td>Xylocaine</td>
<td>84.6 (28.4)</td>
<td>83.9 (23.6)</td>
<td></td>
</tr>
<tr>
<td>Proctosedyl</td>
<td>75.2 (27.4)</td>
<td>70.6 (27.9)</td>
<td></td>
</tr>
<tr>
<td>Nitroglycerine</td>
<td>81.8 (21.1)</td>
<td>54.1 (22.5)*</td>
<td></td>
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</tbody>
</table>

Values as mean (SD)

*p <0.0001 compared to pre-treatment value; paired t-test

Table 3: Number (%) of patients with pain relief and with healed fissure after treatment

<table>
<thead>
<tr>
<th>Study drug</th>
<th>Vaseline (n=16)</th>
<th>Xylocaine (n=16)</th>
<th>Proctosedyl (n=16)</th>
<th>GTN* (n=16)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pain relief at</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2 weeks</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>6 (38)</td>
</tr>
<tr>
<td>4 weeks</td>
<td>0</td>
<td>1 (6)</td>
<td>1 (6)</td>
<td>15 (94)</td>
</tr>
<tr>
<td>6 weeks</td>
<td>4 (25)</td>
<td>11 (69)</td>
<td>12 (75)</td>
<td>15 (94)</td>
</tr>
<tr>
<td>Healing of fissure at</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2 weeks</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>4 weeks</td>
<td>0</td>
<td>1 (6)</td>
<td>1 (6)</td>
<td>3 (19)</td>
</tr>
<tr>
<td>6 weeks</td>
<td>4 (25)</td>
<td>11 (69)</td>
<td>12 (75)</td>
<td>15 (94)</td>
</tr>
</tbody>
</table>

GTN: Nitroglycerine

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including bleeding, perianal bruising, stranguoation of associated prolapsed piles, perianal infection, Fournier's gangrene and full-thickness rectal prolapse. Also, bacteremia occurs in up to 8% of patients.1

Nitric oxide has been shown to be an important inhibitory neurotransmitter in the internal anal sphincter. Reversible chemical sphincterotomy may be achieved by application of an ointment containing GTN, a nitric oxide donor. GTN ointment has been reported to heal anal fissure by inducing sphincter relaxation and improving anodermal blood flow.2,3,4 Whereas an Indian study with GTN showed a success rate of 70%,5,10 many series have shown success rates exceeding 80%.6-11 No study has prospectively compared the efficacy of GTN with other commonly used preparations.

We found a reduction of 34% in MRAP 20 minutes after application of GTN ointment, whereas vaseline, xylocaine and Proctosedyl produced no significant change in MRAP. These results are similar to those reported in placebo-controlled trials of GTN.2,3,4,11 However, one study showed no decrease in anal pressures with GTN in chronic anal fissure.12 Reduction in anal pressure in chronic anal fissure has been shown to increase anodermal blood flow with resultant pain relief and early healing.2,4,13

In our study, complete pain relief occurred much earlier and in more patients with nitroglycerine ointment than with vaseline, xylocaine or Proctosedyl. However, a large multi-center, randomized, controlled trial on 132 patients failed to demonstrate any superiority of GTN over placebo in healing rates and pain scores, although the beneficial effects of GTN on anodermal blood flow and sphincter pressures were confirmed.12 The two series reported until date that compared GTN with xylocaine also showed that pain relief was superior with GTN.15,16

In our study, GTN produced pain relief long before fissure healing; whereas with vaseline, xylocaine and Proctosedyl, pain relief and fissure healing paralleled each other. Although the three non-GTN groups showed no significant decrease in MRAP, a significant number of patients showed healing of the fissure at 6 weeks, indicating that increased sphincter tone may not be the only factor in the pathogenesis of chronic anal fissure.

In contrast with other studies,17 headache was not a significant problem with GTN. We used twice-daily GTN compared to thrice-daily in other studies.

Our study suggests that topical GTN produces successful chemical sphincterotomy. Pain relief and healing of fissure was also seen earlier with GTN. GTN should therefore be considered as the non-surgical treatment of choice for patients with chronic anal fissure.

References

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