Diseases of the Colon & Rectum

Controlled Dose Delivery in Topical Treatment of Anal Fissure: Pilot Study of a New Paradigm

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PURPOSE: Topical nitroglycerin has been widely used as a means for avoiding surgery in patients with anal fissure. However, nitroglycerin has not been universally accepted for this application because of inconsistency of efficacy and side effects. This study compares conventional digital application with precise intra-anal dosing of nitroglycerin using a specialized dose-delivery device and anal cannula. METHODS: Twenty-six consecutive patients (13 males) with chronic anal fissure and no previous treatment were randomly allocated to receive 0.75 ml of 0.3 percent nitroglycerin ointment (2.25 mg nitroglycerin) *t.i.d.* intra-anal using the cannula (Group A) or perianally with the gloved finger (Group B). Nitroglycerin dosage was controlled in Group A by the dose-delivery device connected to the cannula and by single-dose preloaded syringes in Group B. RESULTS: Anal manometry: pressure reduction after application of nitroglycerin was 47 ± 18.6 in Group A and 20.7 ± 13.4 percent in Group B ($P < 0.01$). Headaches were reported by 1 of 10 patients in Group A and 10 of 12 patients in Group B ($P = 0.0027$). Seven patients of Group B had to be crossed to intra-anal treatment as a result of intensity of headaches. Pain relief was noted by 8 of 10 and 9 of 12 patients in Groups A and B, respectively ($P = 0.6$). Sphincterotomy was required in only 13.6 percent of all patients. CONCLUSIONS: Controlled intra-anal dosing of topical nitroglycerin produces a significantly greater reduction in sphincteric pressure and lower incidence of headaches than with perianal administration of the same dose of ointment. These results suggest a new paradigm for increasing safety and efficacy of dose-dependent prescription anal topical medications. [Key words: Nitroglycerin; Dose delivery; Intra-anal; Perianal; Cannula; Manometry]

Topical agents have been widely used in recent years as a means for avoiding sphincteric surgery in patients with chronic anal fissure.[1] These topical agents comprise several classes of compounds that are capable of temporarily reducing internal anal sphincter tone and increasing anodermal blood flow,[2,3] thereby affording relief of pain and allowing healing of the fissure in many patients.[4,5] Topical nitroglycerin (NTG) has been the compound most frequently prescribed in this context.[6–8]

NTG has not been universally accepted as a topical treatment for anal fissure, primarily because of inconsistency of efficacy and side effects, particularly headaches.[9,10] Recommended treatment regimens have customarily included open-ended applicators or inexact digital application, often with the ungloved finger. We have postulated that imprecision of both the dose and focus of topical medications have been responsible for variability in results and side effects, especially headaches.[11]

This study describes dose-regulated administration of NTG using a controlled dose-delivery device (DoseRite™, OrigynRx, Tustin, CA), and intra-anal application of 0.75 ml of 0.3 percent NTG through an end-occluded, side-slotted cannula (AccuTip™, OrigynRx)[12] with an "occlusive" flange (Fig. 1). Because of the construction of the tip, delivery of medication is primarily to the anoderm.

The authors have participated in design, development, and commercialization of DoseRite™ and AccuTip™, patent-pending products of OrigynRx, Tustin, California.

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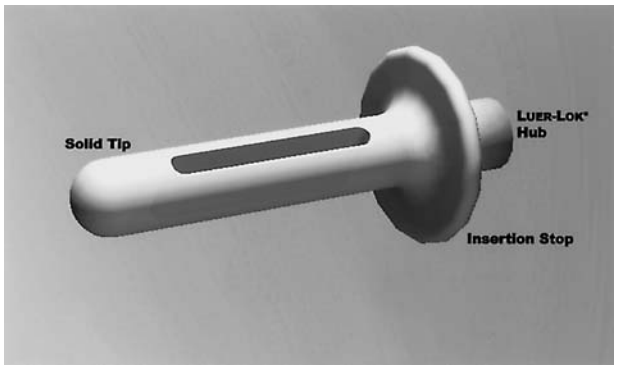


Figure 1. The AccuTip™, an end-occluded, side-slotted cannula for intra-anal administration of topical medication.

PATIENTS AND MATERIALS

Twenty-six consecutive patients (13 males) with chronic anal fissure and no previous treatments were randomly allocated on initial consultation to receive NTG intra-anally with an end-occluded, side-slotted flanged cannula (AccuTip™; Group A) or perianally with their finger, wearing a latex protective cover (Group B). Both groups received the same dose *t.i.d.* of 0.75 ml 0.3 percent NTG (2.25 mg NTG), which was controlled by a device (DoseRite™) connected to the AccuTip™ in Group A and contained in single-dose preloaded syringes in Group B. Patients in Group A were instructed to wipe off any ointment that might leak outside the anal verge after removal of the cannula if such leakage occurred. Patients in Group B were asked to apply the ointment where the anus feels tight but without pushing the finger inside the anal canal.

Patients' demographics are summarized in Table 1. Ten patients in Group A were followed an average of 59.2 days. Twelve patients from Group B were followed an average of 36.4 days. Four patients (1 in Group A and 3 in Group B) were lost to follow-up after initial consultation and study.

Twenty-one patients (11 from Group A; 10 from Group B) were assessed by anal manometry at the beginning of treatment. Maximum resting pressure (MRP) was measured using the station pull-through technique with the patient in the left lateral position.[12] Then NTG was applied, intra-anally or perianally, and resting pressure was measured for at least three minutes at the same distance from the anal verge at which MRP had been obtained. Reduction in MRP after the application of NTG was recorded during at least five minutes.

Clinical follow-up included assessment of headaches, anal symptoms, and changes of treatment regimens. This was done at office visits, every seven to ten days. Patients were followed until: 1) complete healing of fissure confirmed by proctoscopy, 2) referral for lateral internal anal sphincterotomy, 3) crossover from perianal to intra-anal group, 4) patient withdrawal from the study, or 5) completion of this preliminary study.

Anal pain was scored with the use of a Visual Analog Scale. Intensity of headaches was assessed as mild, moderate, or severe. Treatment was affected only in patients with moderate or severe headaches.

Statistics

Comparison in manometry groups was done with Student's *t*-test. Comparison in the incidence of headache was done with chi-squared test (Yates' correction) and in clinical outcome with Fisher's exact test.

RESULTS

Anal Manometry

Manometric results are summarized in Figure 2. There was no significant difference in basal maximum resting pressure between Groups A and B. Pressure reduction measured after application of NTG was significantly greater in Group A than in Group B ($P < 0.01$).

None of the patients randomized to intra-anal application of NTG complained of discomfort on insertion of the lubricated anal applicator tip (AccuTip™). No patients from the perianal group complained from pain with the application of perianal ointment. There was a significant difference in presentation of headaches during treatment. These were much less frequent among patients from Group A. In seven patients of Group B, intensity of headaches

Table 1.
Patient Demographics

	No. of Patients	Male/Female Ratio	Age (Yr)	Follow-Up (Days)
AccuTip™ (Group A)	11	6/5	45.3	54
Finger (Group B)	15	7/8	39.5	36.4

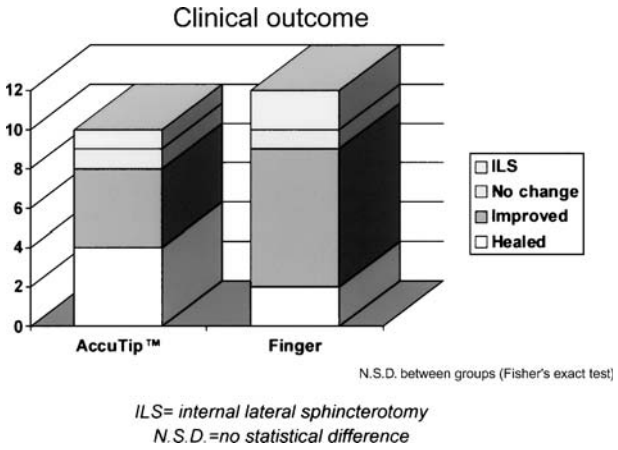
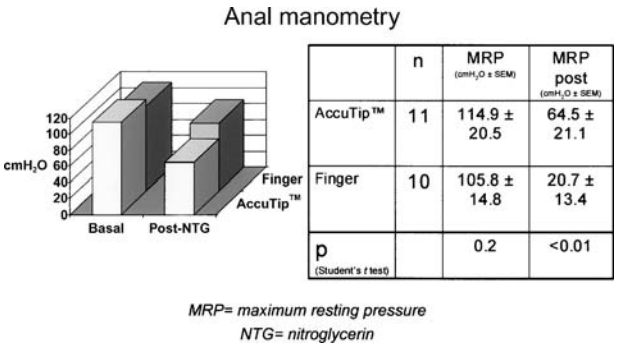


Figure 2. No significant differences were found in clinical outcome between patients using perianal or intra-anal nitroglycerin.



	n	MRP (cmH$_2$O ± SEM)	MRP post (cmH$_2$O ± SEM)
AccuTip™	11	114.9 ± 20.5	64.5 ± 21.1
Finger	10	105.8 ± 14.8	20.7 ± 13.4
p (Student's *t* test)		0.2	<0.01

Figure 3. Maximum anal resting pressure reduction was significantly greater after application of intra-anal nitroglycerin compared with perianal digital application.

made it necessary to cross them to intra-anal treatment, because they refused to continue with the digital application. Six of seven of these patients noted improvement or disappearance of headaches after changing from perianal to intra-anal application (Table 2).

Clinical Outcome

Clinical improvement (sustained pain reduction or healing of the fissure) was noted at the time of follow-up by 8 of 10 patients in Group A, of which 4 were completely healed, and by 9 of 12 patients (P = 0.6) in Group B, of which 2 were completely healed (Fig. 3). One patient in Group A and two patients in Group B were referred for internal lateral sphincterotomy (P = 0.54).

DISCUSSION

Dose-controlled and focused intra-anal administration of topical NTG ointment produces a significantly greater manometric pressure drop and significantly lower incidence of headaches than with perianal administration of the same dose of ointment. The explanation for this finding is difficult, because it would be expected that headaches would occur more easily through the application of NTG on thin, nonkeratinized anoderm than on thicker skin. Although logic suggests that absorption should be poorer through keratinized skin, some patients described immediate and intense headache after applying the ointment without using the protective finger cover. This, too, is difficult to explain, because the keratinized skin of the fingertip is supposed to be thicker than the thoracic skin where topical NTG often is applied for ischemic heart disease.

The observed differences in the proportion of headaches are even more significant after crossing patients with severe symptoms while on perianal NTG to intra-anal application of NTG, because all of them described their subsequent improvement with intra-anal therapy as "significant" or "complete."

Paralleling reductions in sphincteric pressures with intra-anal administration, control of symptoms also seemed more effective with intra-anal administration of NTG, although figures were too small to reach statistical significance. Additional studies are in progress to expand on these promising differences in therapeutic efficacy.

Although follow-up time was not significantly different between the two groups, longer follow-up was achieved in patients treated with intra-anal NTG than

Table 2.
Headaches

	No. of Patients	Headaches	Crossover to the Other Group	Headaches After Crossover
AccuTip™ (Group A)	10	1	—	—
Finger (Group B)	12	10[a]	7	1

[a] P = 0.0027 (chi-squared, Yates' correction).

with digital application. We believe that this is the result of better patient compliance in this group of patients because of their lower incidence of headaches and greater reduction in symptoms. The low overall incidence of sphincterotomy (13.6 percent) underscores the relevance of accurate dosing for this application.

Historically, reports of topical treatment of anal fissure using NTG have been flawed by inconsistency of dosing and focus of topical administration.[13,14] Rectal applicators are usually open-ended, allowing antegrade and retrograde spillage. Digital application often is impossible when fissure pain is the greatest, so many patients simply apply the medication on the perianal skin, allowing for absorption by the perianal skin. Headaches may be worse in patients who choose to apply the medication barehanded, thus enhancing cutaneous absorption by the exposed digit. The fact that headaches were greater and sphincteric pressure reduction was less with digital application in our patients suggests both a reduction in efficacy and an increase in side effects with digital application, even with the protection of gloving.

CONCLUSIONS

Controlled intra-anal dosing of topical NTG affords a new paradigm for increasing the predictability of efficacy and side effects in topical treatment of anal fissures. These same principles may be applicable to other dose-dependent topical anal medications.

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