Topical nitrates potentiate the effect of botulinum toxin in the treatment of patients with refractory anal fissure

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Abstract

Background—Anal fissure is perpetuated by high sphincter pressures and secondary local ischaemia. Pharmacological approaches include topical nitrates and botulinum toxin (BT) which act to reduce anal pressure. BT lowers anal pressure by preventing acetylcholine release from nerve terminals while topical nitrates act by donating nitric oxide (NO). The aims of the present study were to compare the therapeutic effect and lowering action on internal anal sphincter pressure of BT injection and local application of isosorbide dinitrate (ID) compared with BT given alone, in patients with chronic anal fissure (CAF) refractory to treatment with ID.

Methods—Thirty consecutive patients with CAF who did not respond to previous topical ID treatments were randomly assigned to receive one of the following treatments: group A, injection of BT (20 U into the internal anal sphincter) and subsequent daily applications of ID (2.5 mg three times daily for three months); and group B, BT injection only (20 U). If at the end of six weeks following BT injection no improvement was seen in group B, ID was added. A series of anal pressure measurements, including resting basal pressure and resting pressure following topical ID (1.25, 2.5, and 3.75 mg), was carried out both before and after 20 U of BT injection into the internal anal sphincter. At the end of the trial, patients were followed up for an average period of 10 months.

Findings—At six weeks the fissure healing rate was significantly higher in group A patients (10/15 (66%)) compared with group B (3/15 (20%)) (p=0.025). At eight and 12 weeks, no significant differences were seen: 11/15 (73%) v 11/15 (73%) and 9/15 (60%) v 10/15 (66%), group A v group B, respectively. Maximum anal resting pressure (MARP) was significantly lower two weeks after BT injection than baseline MARP (90 (4) v 110 (5) mm Hg; p<0.001). A significantly greater reduction in MARP following local application of ID was achieved after BT injection compared with that achieved before BT injection (p=0.037).

Interpretation—(1) Combined BT injection and local application of ID in patients with CAF who failed previous treatment with ID was more effective than BT alone.

This treatment modality appears to be safe and promising. (2) ID application induced a greater reduction in MARP following BT injection compared with ID application before BT injection. The improved potency of ID on MARP after BT injection suggests a primary cholinergic tonus dominance in some patients and not, as previously claimed, anal sphincter insensitivity to nitrates.

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Keywords: nitrates; botulinum toxin; anal fissure

Anal fissure is a painful longitudinal or elliptical ulcer in the anoderm, extending from below the dentate line to the anal verge. In patients with fissures, basal anal pressure is significantly elevated. Current evidence suggests that idiopathic anal fissures are caused by high internal anal sphincter (IAS) pressure and secondary local ischaemia. Acute anal fissure heals spontaneously or with conservative treatment within six weeks, whereas chronic anal fissure is more intractable and is unlikely to heal with conventional conservative management. Surgical reduction of resting pressure is the recommended treatment. However, the procedure may be associated with permanent impairment of continence. In vitro and in vivo studies in animals have established that nitric oxide (NO) is probably the most important inhibitory neurotransmitter in the IAS. Evidence suggests that organic nitrates such as isosorbide dinitrate (ID) and glyceryl trinitrate are converted to NO by a common enzyme. Glyceryl trinitrate cream applied locally to the anus has been shown to cause lowering of IAS pressure in healthy subjects and to promote healing of anal fissures. The other pharmacological approach involves the use of botulinum toxin (BT). Again, the aim is to decrease resting anal pressure, in this case by preventing release of acetylcholine from presynaptic nerve terminals. Maria et al reported a 73% healing rate two months after BT injection into the IAS. BT and local nitrates lower resting pressure by different mechanisms: we therefore decided to use them simultaneously in the treatment of patients with refractory chronic anal fissure (CAF). The aims of the present study were to

Abbreviations used in this paper: BT, botulinum toxin; NO, nitric oxide; IAS, internal anal sphincter; ID, isosorbide dinitrate; CAF, chronic anal fissure; MARP, maximum anal resting pressure.
treat patients with CAF, refractory to treatment with ID, by injection of BT in combination with local application of ID compared with injection of BT alone. We assessed both the therapeutic effects and lowering of IAS pressure of the two treatments.

Patients and methods
Thirty consecutive patients with CAF who did not respond to previous topical ID treatment given over a period of at least six weeks were recruited to participate in the study. Informed consent was obtained from each patient. At study initiation, anal manometry was performed in all patients using a constantly perfused side hole catheter (Sandhill TDS 8000, Highlands-Ranch, Colorado, USA). Basal maximum anal resting pressure (MARP) was recorded 10 minutes after insertion of the catheter. MARP was recorded again 10 minutes after the first dose of 1.25 mg ID to the anus. A further dose of 1.25 mg was then applied. We allowed 10 minutes for stabilisation at each dose increment, and manometric studies were repeated up to a total dose of 3.75 mg ID. We used Isoket spray (Schwartz-Pharma, Germany), which delivers 1.25 mg of ID at each pressure. Squeeze pressure was also recorded. All manometric studies were performed at least 24 hours after cessation of local application of nitrates. At this stage type A botulinum toxin (Botox, Allergan, Ireland) was diluted in saline to 40 U/ml: 10 U of dilute BT was injected with a 27 gauge needle into the IAS on both sides lateral to the fissure (total dose 20 U) in all patients.

Patients were randomly divided into two treatment groups: group A, BT injection and subsequent daily applications of ID spray (2.5 mg three times daily) for three months; and group B, BT injection only. If at the end of six weeks following BT injection, no improvement was seen in group B patients, ID was added as in group A.

Following BT injection, all patients were evaluated at two week intervals for a period of three months. All patients were reexamined and questioned about side effects and level of pain experienced on defecation. On the first follow up visit, two weeks after BT injection, the same manometric studies as described above were repeated. Thereafter, the healed patients were contacted by telephone every three months and were encouraged to keep in contact if symptoms recurred.

STATISTICAL STUDIES
Age, symptoms duration, and time to healing are expressed as mean (SEM). Variables in groups A and B were compared using the Student’s t test and non-parametric Mann-Whitney test, when appropriate. Fisher’s exact test was used to compare the success rate between groups A and B. The effect of 3.75 mg of ID on the decrease in MARP was tested before and after BT injection using a matched pairs two sided t test.

Results

BASELINE ASSESSMENT
Group A comprised 15 patients (six men, nine women), mean age 43.9 (3) years (range 21–67). Symptoms had been present for a mean period of 18.2 (3) months. Group B also comprised 15 patients (six men, nine women), mean age 45.3 (4) years (range 24–72). Symptoms had been present for a mean period of 21.1 (3) months. MARP was 109 (6) mm Hg in group A and 109 (7) mm Hg in group B (NS). The maximum voluntary squeeze pressure in group A was 89.1 (9) mm Hg and in group B 80.5 (9) mm Hg (NS).

FISSURE RESPONSE
At six weeks, the fissure healing rate was significantly higher in group A patients: 10/15 (66%) v 3/15 (20%) in group B (p=0.025). At six weeks, ID was added to the non-responders of group B, and at eight and 12 weeks no significant differences were seen: 11/15 (73%) v 9/15 (60%) and 11/15 (73%) v 10/15 (66%) (group A v group B, respectively) (fig 1). Mean time for pain relief was 11.4 (2) days in group A and 18.3 (5) days in group B (NS). During follow up, one patient in each group relapsed; this occurred four and six weeks after healing. Three patients who had not healed at three months received a second BT injection of 25 U: this was also unsuccessful and those patients then underwent lateral sphincterotomy. The other treatment failures refused to be operated on because they were symptom free or only mildly symptomatic. Side effects occurred in one patient who had perianal thrombosis following BT injection and two patients had mild transient headache following ID application.

MANOMETRIC STUDIES
MARP was significantly reduced two weeks after BT injection: 24.2 (4)% in group A and 20.6 (2)% in group B (NS). The pressure decreased in both groups from 110 (5) mm Hg before injection to 90 (4) mm Hg after injection (p<0.001). Significantly greater reductions in MARP following different doses of topical ID were achieved after BT injection compared with the reductions before BT injection (p=0.037) (fig 2). Maximum voluntary pressure decreased by 4.8 (1)% and 4.4 (1)% in groups A and B, respectively (NS).
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Injected. Hence the success rate in the
anism di
crease in pressure with
indicate decreases in IAS pressures after 1.25, 2.50 and
patients in the study before treatment. ID1, ID2, and ID3
(MARP) by isosorbide dinitrate (ID) and botulinum toxin
Figure 2 Decrease in maximum anal resting pressure

Discussion
Local nitrates can assist anal healing by reduc-
ing anal pressure and inducing local vasodilata-
BT relaxes the anal sphincter by a mech-
nism different from that of local nitrates: therefore, we decided to admin-
ID. The first purpose of the study was to com-
paring the therapeutic efficacy of combined
treatment with BT and ID with that of BT alone. At six weeks, the fissure healing rate
was significantly higher in patients who received
the combined treatment compared with patients
treated with BT alone. At six weeks, ID was
added to those patients treated with BT alone
who failed to heal. At eight and 12 weeks,
no significant difference was seen between
groups. Hence addition of topical ID at six weeks
to non-responders (or very slow responders) in
group B induced faster fissure healing.
The overall success rate in both groups at the
deal of the drug. In contrast, drug tolerance was not
a problem in reducing IAS pressure. One
patient had perianal thrombosis following BT
injection. Incontinence problems were not
reported by any patient despite very low
MARP levels (sometimes to 30 mm Hg)
induced by the treatment. This can be
explained by the relatively young age of our
patients and their well preserved continence.

The second purpose of the study was to
evaluate the lowering effect on MARP of either
BT alone or ID application before and after BT
injection. The mean decrease in MARP
following 2.5 mg ID alone was 17.2%: this
value is lower than that achieved in the success
group in our previous study (32%) and is similar
to the failure group in that study (16%).
Following BT injection alone, MARP
decreased significantly. When ID application was
given after BT, MARP decreased significantly
more than when ID was given before BT injec-
tion (see fig 2).

No significant differences were found when
baseline MARP or its percentage decrease follow-
ing treatment were compared between
responders and non-responders. However,
chronic fissure changes were more prominent
in non-responders, suggesting that abundant
fibrous tissue was a dominant factor that may
negatively influence fissure healing despite sig-
ificant pressure reduction rates.

Watson et al found that patients with CAF
who did not respond to nitrate treatment had a
smaller reduction in pressure following nitrate
application compared with responders and
healthy controls. They concluded that the
pathogenesis of CAF and the cause of the failure
to heal following nitrate treatment is related, at
least in part, to an insensitivity of the IAS to
endogenous and exogenous NO, respec-
tively. However, our results suggest a primary
cholinergic tonus dominance in some patients
as the relaxing effect of NO could be fully
expressed following cholinergic block with BT.

We conclude that ID potentiates the thera-
peutic effect of BT in patients with refractory
chronic anal fissure. The significantly
improved pressure lowering effect of ID follow-
ing BT injection compared with its lowering effect
before BT injection suggests a primary cholin-
ergic tonus dominance in patients with refrac-
tory anal fissure.

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References

1 Farouk R, Dubois G S, MacGregor A, et al. Sustained inter-
nal sphincter hypertonia in patients with chronic anal
2 Greenfield LJ, Mulholland MW, Oldham KT, et al. Surgery:
scientific principles and practice. Philadelphia: JB Lippincott,
3 Klosterhalfen B, Vogel P, Rixen H, et al. Topography of the
inferior rectal artery: a possible cause of chronic primary
4 Schouten WR, Briel JW, Auwerda JJ. Relationship between
anal pressure and anoderm blood flow: the vascular patho-
5 Fleshman JW. Anorectal motor physiology and pathophys-
6 Vafai M, Mann CV. Closed lateral internal anal sphinc-
terotomy as an office procedure for the treatment of anal fiss-
7 Chakker S, Rattan S. Release of nitric oxide by activation of
nonadrenergic noncholinergic neurons of internal anal