Botulinum toxin versus botulinum toxin with low-dose glyceryltrinitrate for healing of chronic anal fissure: a prospective, randomised trial

Muhammad Asim, Neil Lowrie, Joanna Stewart, Simi Lolohea, Ralph Van Dalen

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Abstract

**Background** Chronic anal fissure (CAF) is perpetuated by high sphincter pressures and secondary local ischemia. Pharmacological approaches include topical nitrates and botulinum toxin (BT), which both help to decrease the sphincter pressure.

**Aims & Objectives** The aims of the present study were to assess the efficacy and safety of BT injection and combined treatment with BT injection and lowered dose glyceryltrinitrate (GTN) cream for the treatment of CAF. We hypothesised that combined treatment would have a synergistic effect on healing.

**Methods** Forty-one consecutive patients with CAF were randomly assigned to receive one of the following treatments: Group A, injection of BT (20 U into internal anal sphincter) and Group B, BT injection (20 units) and subsequent thrice daily topical applications of half-dose 0.2% GTN cream for 6 weeks. Patients were followed up at 6 and 12 weeks and were assessed for healing of anal fissure, by means of visual inspection using fissure grades; for faecal incontinence, using Cleveland Clinic incontinence scores; and for fissure pain & headache using a numeric pain rating scale.

**Results** Fissure healing was similar in the two groups at both 6 (30% in BT and GTN and 33% in BT only) and 12 weeks (50% in BT and GTN vs 57% in BT-only group). Neither the change in pain score from 6 to 12 weeks, nor the overall level of pain was significantly different in the 2 groups. Moderate or severe headaches were suffered by 58% of patients using GTN.

**Conclusion** Single-agent treatment by means of BT injection alone was well tolerated compared with combination treatment with BT injection and GTN cream, with no significant differences in healing of CAF observed in this small study.

Anal fissure is one of the most common benign anorectal conditions, which may result from high anal sphincter pressure, especially high internal anal sphincter (IAS) pressure. The goals of therapy are to break the cycle of sphincter spasm and tearing of anal mucosa & to promote healing of fissure.

Medical therapy is successful in the majority of patients with surgery reserved for refractory cases.¹ Acute anal fissure usually heals spontaneously or with conservative treatment within 6 weeks, whereas chronic anal fissure is more intractable and is unlikely to heal with conventional conservative management.²
Surgery by means of lateral internal sphincterotomy (LIS) carries the risk of permanent faecal incontinence. The risk has varied among reports from as low as 0 to as high as 24 percent. In-vitro and in-vivo studies in animals have established that nitric oxide (NO) is probably the most important inhibitory neurotransmitter in IAS. Glyceryltrinitrate (GTN) 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. Another non-surgical agent for treatment for anal fissure is botulinum toxin (BT; ‘botox’) which decreases the anal pressure by preventing release of acetylcholine from presynaptic nerve terminals. Maria et al reported 73% healing for anal fissure after single application of BT injection.

There is only one study previously by Lysy et al looking at the synergistic effect of BT and topical nitrates (isosorbide dinitrate) for healing of chronic anal fissure, which showed significantly higher healing, 66%, in the combined treatment group compared to BT alone, 20%.

Scholefield et al conducted a dose finding study with different strengths of GTN for chronic anal fissure and found that 0.1% GTN cream has a higher healing rate compared to 0.2% cream, with a smaller percentage of patients reporting headaches: 18% versus 36% with 0.2% GTN cream.

The aims of the present study were to assess the efficacy & safety of BT injection and combined treatment with BT injection and lowered dose 0.2% GTN cream for the treatment of CAF (equivalent to 0.1% GTN if used in half the recommended dose). We hypothesised that combined treatment would have a synergistic effect on healing and lowered dose GTN would help with patient compliance as GTN application is associated with severe headaches in some patients.

Patients and Methods

Forty-one consecutive patients with chronic anal fissure (CAF) from the Waikato region of New Zealand, with ages ranging from 18–80 years, were recruited to participate in a study over the period of 21 months from March 2010 to December 2011. Exclusion criteria were: previous surgical treatment for anal fissure, pregnancy (current or planned in next 6 months) and lactation, inflammatory bowel disease, rectal or anal malignancy, unable to self-administer medications, unable to complete necessary trial documentation or unable to attend necessary clinical follow-up, any history of unexplained syncope or orthostatic hypotension, history of faecal incontinence, tuberculosis, HIV/AIDS, syphilis, perianal sepsis or fistulas, immunosuppressant and use of sildenafil or other nitrate preparations for ischaemic heart disease (IHD).

After initial assessment and informed consent, patients were randomly assigned into two groups (using computer-generated randomisation codes):

- **Group A**: Botox (BT) only group.
- **Group B**: Botox plus low-dose GTN group.

Patient allocation was concealed and study was unblinded. Group A participants were given an injection of 20 units of Botulinum toxin type-A (Botox®, Allergan New Zealand Ltd) using 25G needle into the internal sphincter at 3 and 9 o’clock positions (10 units on each side) while in the left lateral position by a single colorectal surgeon (internal anal sphincter was felt with gloved finger, no EMG guidance used).

Group B were given BT injection and were also prescribed 0.2% GTN cream (Rectogesic) to use in half the recommended dose (0.5cm), to be applied topically thrice daily around the fissure area using
an applicator for 6 weeks. Patients were evaluated at 6 and 12 weeks in a fissure clinic using a standardised questionnaire.

The study questionnaire included age, sex, ethnicity and BMI. Fissure pain and headache severity were recorded using a numeric pain scale with range of 0-10 with zero being no pain and 10 as worst pain. Headaches were categorised as mild (1–3), moderate (4–7), and severe (8 and higher). Absence or presence of per-rectal bleeding with fissure was also recorded. Flatus and faecal incontinence was graded using the Cleveland clinic incontinence score.9

Fissure healing was assessed by visual inspection of the fissure area using fissure grades 0-4 (grade 0 = healed, grade 1 = fissure with exposed internal anal sphincter (IAS), grade 2 = deeper fibres with widely exposed IAS, Grade 3 = deep undermined fissure, Grade 4 = associated perianal fistula).10 Patient compliance with GTN cream was assessed based on detailed history on first follow up visit.

This study was approved by northern Y – Regional Ethics Committee, New Zealand and was registered with Australian New Zealand Clinical Trials Registry (ANZCTR) with registration number: ACTRN12613000254796.

Statistical analysis—Based on previous study7 we hypothesised that the BT and GTN group would have 30% higher healing rate compared with BT alone. We aimed to recruit 80 patients over 1 year. (based on power calculation). To detect a 30% difference in healing between BT and GTN versus BT-alone group we require over 38 subjects per group with 80% power to detect a real different, at the 5% level of significance. By the end of 21 months we were not able to recruit more than 50 patients into our study and based on analysis done at that point showing no difference, we decided to close the study.

As only one patient reported headaches at 12 weeks the difference in headache in the two treatment groups was only examined at 6 weeks. To look at the difference in the occurrence of headache in the two groups at 6 weeks a logistic regression was run with headache or not as the outcome and headache scores at baseline and group as explanatory variables.

To investigate whether there was a difference in the fissure pain in the two groups, a generalised linear mixed model was fitted with pain, categorised as none, 1–5 or 6–10 as the ordinal outcome and pain at baseline, group, time and the group time interaction as explanatory variables. Subject was included as a random effect to allow for the within person correlation. All subjects with data recorded after baselines were included in the analysis.

A sensitivity analysis was run to investigate whether the results of differences in change in fissure pain were influenced by those not completing the study (needing intervention before study completion). A Mann Whitney U test was performed, including all subjects enrolled into the study, using their last recorded fissure pain score.

For those who completed the study this was their 12-week follow-up measure but for those who withdrew during the first 6 weeks for extra intervention it was the score recorded before this extra intervention. For 2 subjects who withdrew early there were no measures taken post baseline so their baseline measure was used.

Results

Forty-one consecutive patients with CAF were recruited into the study over a 21 months period and were randomly assigned to group A (BT alone,) 21 patients, and Group B (BT & GTN), 20 patients. Patient demographics are shown in Table 1.

Table 1. Patient demographics

<table>
<thead>
<tr>
<th>Variables</th>
<th>Group-A (BT alone)</th>
<th>Group-B (BT &amp; GTN)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age mean (SD*) (range)</td>
<td>41 (14) (18–70)</td>
<td>42 (13) (21–80)</td>
</tr>
<tr>
<td>BMI** mean (SD)</td>
<td>28 (6)</td>
<td>27 (6)</td>
</tr>
<tr>
<td>Sex</td>
<td>5 male, 16 female</td>
<td>11 male, 9 female</td>
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*Standard deviation; **Body mass index; BT=Botox (botulinum toxin); GTN= glyceryltriminrate.
Three patients (14%) from group A did not complete the study; one had surgery at 6 weeks due to severe symptoms and two had repeat BT injections before 6 weeks for severe symptoms. All had data recorded immediately before surgery or injection which was included as their 6-week measure.

Five patients (25%) from Group B did not complete; one had surgery due to severe symptoms at 4 weeks, one could not tolerate GTN and didn’t come for follow up, 3 had repeat BT injections for severe symptoms before 6 weeks. There was no data recorded after baseline for the subject who could not tolerate GTN or for one of those requiring a further injection.

The difference in withdrawal rate in the 2 groups was not statistically significant (p=0.39) Eighteen patients in Group A and 15 patients in Group B completed the study (Figure 1).

Figure 1. Anal fissure study flow diagram

Fissure pain—A difference in the change in pain from 6 to 12 weeks in the 2 treatment groups could not be shown (p=.44). The interaction was therefore removed from the analysis. No difference in the pain post treatment in the 2 groups could be shown (p=0.75) (Table 2). This result was not altered when the influence of non-completion was investigated by comparison of the subjects last recorded measure in the 2 groups (p=0.41).
Table 2. Median (interquartile range) fissure pain scores after botox alone and botox & GTN

<table>
<thead>
<tr>
<th>Group A (BT alone)</th>
<th>Group B (BT &amp; GTN)</th>
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<tbody>
<tr>
<td>Baseline</td>
<td>7 (6–8)</td>
</tr>
<tr>
<td>6 weeks</td>
<td>2 (0–5)</td>
</tr>
<tr>
<td>12 weeks</td>
<td>0 (0–5)</td>
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**Fissure healing**—Fissure healing was similar in both groups at 6 weeks, 30%, 95% CI 12–54% (6 patients) in BT & GTN group (assuming the 2 the patients who withdrew without 6 week data were unhealed) compared to 33% 95% CI 15–57% (7 patients) in BT only group.

Fissure healing amongst those completing the study was the same in both groups at 12 weeks, with 10 completely healed at 12 weeks out of 15 in BT and GTN group (67%, 95% CI 38–88%), compared to 12 patients completely healed out of 18 in BT only group (67%, 95% CI 41–87%). Including those who withdrew from the study as failures these percentages would be 57% healed in group A and 50% in group B.

**Fissure severity/grades**—In the BT alone group, of the 18 patients who completed the study 14 patients had grade I fissure, 3 had grade II and 1 had grade III fissure at the start of study. At 12 weeks 12 patients were healed completely with fissure grade down to zero and the 6 unhealed patients had only grade I fissure. Of the patients who had grade II and III fissures at baseline only one remained unhealed at 12 weeks with fissure grade reduced to grade I.

In the BT plus GTN group 13 patients out of 15 patients who completed the study had grade-I fissure, one patient each had grade II and grade III fissures at the start of the study. 10 patients were completely healed at 12 weeks with fissure grade down to zero and the remaining 5 patients had only grade I fissure which remained unhealed, including the 2 patients with grade II and III at baseline.

**Headache with GTN therapy**—There was evidence of a difference in the presence of headache in the two groups at 6 weeks (p=0.03) with those in the GTN group more likely to have a headache.

Four patients in the GTN group had severe headache while 7 reported moderate, 4 mild and 4 no headache. This was not recorded for 1 patient. Only one of those in the Botox only group reported headaches at 6 weeks (severe) and they also reported severe headache at baseline. Overall 79% of patients receiving lowered dose GTN treatment reported headache at 6 weeks with 58% reporting moderate or severe headache and 63% reporting a more severe score than reported at baseline.

**Faecal/flatus incontinence**—Only three patients in the BT-alone group had temporary incontinence at 6 weeks with CCIS of 1, 3 and 7 (all mild). None of the patients in the BT plus GTN group reported incontinence at any point of time. A statistically significant difference could not be demonstrated (p=0.1)
Discussion

Both BT and topical nitrates work by different mechanisms. One previous study by Lysy et al. investigated the combined effect of BT and Isosorbide dinitrate (ID) on healing of chronic anal fissure. They found that combined treatment had a higher healing rate than BT alone at 6 weeks. They then crossed the patients from BT alone to receive ID and both had similar healing rates at 12 weeks.7

In our study we used glyceryltrinitrate (GTN) instead of ID and used it in half the recommended dose to decrease the headaches associated with treatment.12 Healing on visual inspection of fissure area was similar in both groups at both 6 weeks and 12 weeks. Also no difference in pain scores in the two groups could be shown, with the median pain score similar at 6 weeks and the same at 12 weeks in those that completed the study.

Although more subjects in the group receiving GTN withdrew from the study because of severity of symptoms this difference could not be shown to be likely to represent a real difference and their withdrawal did not appear to have an important influence on the difference in fissure pain or healing in the 2 groups. Fissure healing with BT in our study was comparable with results from Lysy et al.7

Patients who received combined treatment were expected to have more transient faecal incontinence as both BT and GTN relax the anal sphincter but none of the patients using GTN suffered from transient faecal incontinence in our sample. In regards to headaches, in those using GTN; 79% reported suffering from headaches, 63% of greater severity than at baseline with 21% reporting severe headache including one patient in the GTN group who dropped out because of severe headaches. Altomore et al reported a 23% headache rate associated with GTN treatment.12

We conclude that single agent treatment by means of BT injection alone is well tolerated and has a similar response rate to those treated with a combined treatment of BT injection and GTN cream.

We found no significant side effects in those treated with BT alone while even with lowered dose of GTN, about three-quarters of the patients experienced headaches in the combined BT injection and GTN cream treatment group. We measured the patient compliance with GTN cream based on detailed patient history only; this may a possible limitation as patients getting severe headaches with GTN may have not used the cream regularly. Using GTN placebo control would have been an ideal to compare two groups. Mild temporary incontinence in BT alone group was not clinically important.

Twenty percent of the patients in our study dropped out due to severe symptoms and ended up getting surgery or a repeat BT injection. Although we found no indication of a synergistic effect on healing of anal fissures by combining BT and topical nitrates, our study was small so such an effect should not be ruled out without a larger study to confirm or otherwise the validity of our results.
Competing interests: Nil.

Author information: Muhammad Asim, Surgical Registrar, Waikato Hospital, Hamilton; Neil Lowrie, Surgical Registrar, Waikato Hospital, Hamilton; Joanna Stewart, Biostatistician, School of Population Health, University of Auckland; Simi Lolohea, Colorectal Surgeon, Waikato Hospital, Hamilton; Ralph Van Dalen, Colorectal Surgeon and Director of General Surgery, Waikato Hospital, Hamilton

Correspondence: Dr Muhammad Asim, General Surgery, Waikato Hospital, 222 Pembroke Street, Hamilton 3204, New Zealand. Email: aasim166@yahoo.com

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