Botulinum toxin vs glyceryltrinitrate for the medical management of chronic anal fissure: a meta-analysis
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CRD summary
This review found botulinum toxin was as effective as glyceryltrinitrate in the management of chronic anal fissures, but it was associated with lower complication rates. The lack of information about the participants and treatment regimens, and the inclusion of three very small trials of limited quality, means that the reliability of the authors’ conclusions is uncertain.

Authors' objectives
To evaluate the effectiveness of botulinum toxin compared with glyceryltrinitrate in the pharmacological management of chronic anal fissure.

Searching
PubMed, EMBASE, CINAHL and the Cochrane Library were searched from January 1980 to March 2007 for relevant studies; search terms were reported. Reference lists of retrieved articles were also searched. The "related articles" function was employed to identify additional studies.

Study selection
Randomised controlled trials (RCTs) that evaluated the use of botulinum toxin and/or glyceryltrinitrate in the treatment of chronic anal fissure were eligible for inclusion. Eligible trials were required to report at least two standardised outcomes. Trials that reported significant cross-over of patients, and those with insufficient data, were excluded.

The included trials had patients of all ages diagnosed using clinical tests, with or without manometry. Glyceryltrinitrate (0.2%) was typically applied twice daily to the distal anal canal and anal margin. Botulinum toxin was given as local injections, but the dose and frequencies of treatments were not outlined in the review. The included trials evaluated anal fissure healing/improvement at eight weeks follow-up. Other outcomes assessed were total side effects, headache, and faecal incontinence.

The authors did not state how many reviewers performed the study selection.

Assessment of study quality
Methodological quality was assessed using inclusion criteria, randomisation, allocation concealment, blinding, stating of cross-over, use of primary and secondary endpoints, and the use of intention-to-treat analyses. The results of the quality assessment were tabulated.

The authors did not state how many reviewers performed the quality assessment.

Data extraction
Two reviewers independently extracted data to permit the calculation of risk ratios (RR) and corresponding 95% confidence intervals (CI) for the outcomes evaluated. Any disagreements between the authors were resolved by mutual agreement.

Methods of synthesis
The pooled risk ratios and 95% confidence intervals were calculated using a Mantel-Haenszel fixed-effect model. The Cochran's Q-statistic was used to evaluate statistical heterogeneity across the trials. In the event of significant heterogeneity, a DerSimonian and Laird random-effects model was used.

Results of the review
Three trials were included in the review (n=180 patients); sample size ranged from 30 to 100. The methodological quality of the included trials was considered to be inadequate, with unclear reporting of allocation concealment and blinding. The mean follow-up ranged from two months to 36 months.

Botulinum toxin and glyceryltrinitrate were found to be equally effective in healing and improving chronic anal fissure, with no statistically significant differences observed in effectiveness, although there was significant heterogeneity across the results of the three trials (Q=4.03; p<0.042).

Treatment with glyceryltrinitrate was associated with a higher incidence of total side effects (RR 0.14, 95% CI 0.05 to 0.40) and headache (RR 0.06, 95% CI 0.01 to 0.30). There was no statistically significant heterogeneity observed for these outcomes.

One trial (n=30 patients) reported a recurrence rate of chronic anal fissure of 33% in the botulinum toxin group and 40% in the glyceryltrinitrate group at a mean follow-up time of three years.

Authors' conclusions
Botulinum toxin was as effective as glyceryltrinitrate in the management of chronic anal fissure, but it was associated with a lower complication rate; it could be recommended as a first-line treatment for chemical sphincterotomy in patients with chronic anal fissure. A major multi-centre randomised controlled trial is required to further establish stronger evidence for this procedure.

CRD commentary
The review addressed a defined question and criteria for inclusion were stipulated. Appropriate electronic databases were searched, but no attempts to minimise publication bias were reported. It was also unclear if there were any language restrictions, so there may a risk of language bias. Steps were taken to minimise errors and bias for data extraction, but methods were not reported for study selection and the assessment of methodological quality.

There was little information on the trial characteristics pertaining to dose regimens. Given this, and the substantial heterogeneity found, the authors' decision to pool the results of the trials may not be justified. The authors correctly acknowledged the limitation of the review in terms of the inadequate methodological quality and the small size of the included trials. The finding of no significant difference does not equate to equality, since there may have been too few patients analysed to detect a significant difference between treatments.

The lack of information about the participants and treatment regimens, and the inclusion of three very small trials of limited quality, mean that the reliability of the authors’ conclusions is uncertain.

Implications of the review for practice and research
Practice: The authors stated that botulinum toxin can be used as a first-line therapy for chemical sphincterotomy in patients with chronic anal fissure, given that patients experience fewer side effects than patients treated with topical applications of glyceryltrinitrate.

Research: The authors stated that a large multi-centre randomised controlled trial is required to confirm the findings from the review and provide a stronger evidence base of this treatment approach.

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