Meta-analysis of randomized and controlled treatment trials for achalasia

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CRD summary
The authors concluded that based on limited evidence, laparoscopic myotomy was the preferred method for treating patients with achalasia. Evidence appeared to support the authors’ conclusions, but the authors acknowledged that evidence was limited and this should be taken into account when interpreting review findings.

Authors' objectives
To evaluate the efficacy and safety of different treatments for achalasia.

Searching
MEDLINE, EMBASE, Cochrane Central Register of Controlled Trials (CENTRAL), LILACS Latin-American and Caribbean Center on Health Sciences Information and Science Citation Index Expanded were searched from inception to March 2008 for studies reported in English. Search terms were reported. Abstracts from major gastroenterology meetings (Digestive Disease Week, United European Gastroenterology Week) and reference lists were screened. Abstracts were excluded.

Study selection
Randomised controlled trials (RCTs) were eligible if they compared different treatment for male and female patients of any age with primary achalasia confirmed using clinical, manometric, radiographic and endoscopic methods. Studies had to assess symptom severity using a modified symptom score that summed scores for dysphagia, regurgitation and chest pain. Studies had to evaluate the following outcomes one-year post-treatment: oesophageal function using oesophageal manometry; remission rates; relapse rates; complication rates; and adverse events. Acceptable definitions of these outcomes were reported in the paper. Studies of patients with co-existing gastric or oesophageal carcinoma or ongoing gastroesophageal reflux disease were excluded.

Interventions compared in more than one of the included studies were: botulinum toxin injection versus pneumatic dilation treatments; botulinum toxin injection versus laparoscopic myotomy; and pneumatic dilation versus laparoscopic myotomy. Seven different comparisons were examined in single studies. Just over half (54%) of patients were male. Where reported, mean age ranged from 26 to 57 years, mean duration of symptoms ranged from 16 to 62 months and mean baseline symptom scores ranged from 4.1 to 18.

Two reviewers independently selected studies. Disagreements were resolved by consensus with the help of a third reviewer if required.

Assessment of study quality
Two reviewers independently assessed validity using the five-point Jadad scale of randomisation, blinding and losses to follow-up. Allocation concealment was assessed. Disagreements were resolved by consensus with the help of a third reviewer if required.

Data extraction
Two reviewers independently extracted data. Disagreements were resolved by consensus with the help of a third reviewer if required.

Methods of synthesis
Where possible, pooled relative risks (RR) and 95% confidence intervals (CI) were calculated using a fixed-effect model in the absence of significant heterogeneity ($I^2 \leq 50\%$); otherwise, a random effects model was used. If studies were too clinically heterogeneous to pool, they were combined in narrative synthesis.

Sensitivity analysis was used to assess clinical remission rates for botulinum toxin injection compared with pneumatic dilation for patients undergoing their first treatment and examine the influence of study quality by analysing only high-
quality studies with adequate allocation concealment, blinding and losses to follow-up.

Results of the review
Seventeen RCTs were included (n=761 reported in text and n=855 in table). Sample size ranged from 17 to 168. Six studies reported adequate randomisation methods. Six studies were single-blinded. All studies reported reasons for withdrawals. Six studies reported allocation concealment.

Botulinum toxin injection versus pneumatic dilation treatments (five studies, n=154): Pneumatic dilation was associated with a significantly higher remission rate (66% versus 36%, RR 2.20, 95% CI 1.51 to 3.20) and significantly lower relapse rate (17% versus 50%, RR 0.36, 95% CI 0.22 to 0.58) than botulinum toxin injection. No significant heterogeneity was found for the clinical efficacy analysis.

Botulinum toxin injection versus laparoscopic myotomy (two studies, n=117): Laparoscopic myotomy was associated with "superior efficacy" at one year compared to botulinum toxin injection (83% versus 65%, RR 1.28, 95% CI 1.02 to 1.59).

Pneumatic dilatation versus laparoscopic myotomy (two studies, n=81 underwent these procedures): Laparoscopic myotomy was associated with significantly higher remission rates (95% versus 78% in first paragraph of text, 82% versus 65% in second paragraph of text and 95% versus 64% in forest plot, RR 1.48, 95% CI 1.16 to 1.87 in both text and forest plot) and a significantly lower relapse rate (5% versus 36% in first paragraph of text, 4% versus 23% in second paragraph of text, RR 0.14, 95% CI 0.04 to 0.58).

There were no differences in one-year remission rates between: nifedipine versus pneumatic dilation (one study, n=30); pneumatic dilation versus pneumatic dilation plus botulinum toxin injection (one study, n=54); or laparoscopic myotomy versus thoracic myotomy (one study, n=168).

Complications and adverse events: Pneumatic dilation treatments were associated with significantly higher complication rates than botulinum toxin injection (19% versus 5%, risk difference 0.15, 95% CI 0.03 to 0.25). The most severe complication was perforation. Thoracic myotomy was associated with a significantly higher rate of gastrointestinal reflux than laparoscopic myotomy (67% versus 17%, p<0.03; one study). Botulinum toxin injection was associated with dysphagia and chest pain. Pneumatic dilation and laparoscopic myotomy were associated with dysphagia and heartburn.

Authors' conclusions
Based on limited evidence, laparoscopic myotomy was the preferred method for treating patients with achalasia.

CRD commentary
The review question was clearly stated and inclusion criteria were appropriately defined. Several relevant sources were searched, but no attempts were made to minimise publication or language bias. Methods were used to minimise reviewer errors and bias in study selection, data extraction and validity assessment. Study validity was assessed and results were reported. Heterogeneity was assessed. Appropriate methods were used for the meta-analyses. There were discrepancies in remission and relapse rates for pneumatic dilatation versus laparoscopic myotomy.

The review was generally well-conducted. Evidence appeared to support the authors’ conclusions but, the authors acknowledged that evidence was limited and this should be taken into account when interpreting review findings.

Implications of the review for practice and research
Practice: The authors stated that patients who had treatment for achalasia should be followed-up regularly so that disease progression can be identified early.

Research: The authors stated that future RCTs should compare the effects of laparoscopic myotomy plus different fundoplication methods versus laparoscopic myotomy alone. Outcomes for assessing different treatments for achalasia should be standardised.
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