Prevention of postoperative recurrence of Crohn's disease

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CRD summary
The authors concluded that only thiopurines and nitroimidazolic antibiotics were able to reduce postoperative clinical and endoscopic recurrence of Crohn's disease. Mesalamine seemed superior to placebo in preventing clinical recurrence. Infliximab seemed superior to placebo in preventing endoscopic recurrence. Variation between studies and a lack of reporting of review methods make the reliability of the conclusions unclear.

Authors' objectives
To evaluate the efficacy of drug regimens and surgical techniques in the prevention of clinical, endoscopic and surgical postoperative recurrence of Crohn's disease.

Searching
MEDLINE and EMBASE databases were searched to July 2010 for articles in English. Search terms were reported. Cross referencing was used to identify additional articles.

Study selection
Randomised controlled trials of medical or surgical interventions for the treatment of patients who had a surgical induced remission of their Crohn's disease were eligible for inclusion. Studies had to report the definition of recurrence and include data on clinical and/or endoscopic and/or surgical recurrence rates (definitions reported in the paper).

Drug therapy interventions included mesalamine, nitroimidazolic antibiotics and thiopurines, buenoside, probiotics, interleukin-10 and infliximab. Surgical interventions included length of resection margin, anastomosis and laparoscopic versus open resection. No details of participants were reported.

The authors did not state how many reviewers selected studies for inclusion.

Assessment of study quality
Study quality was assessed with the Cochrane risk of bias tool. Criteria included adequacy of sequence generation, allocation concealment, blinding, incomplete outcome data addressed and freedom from selective reporting.

The authors did not state how many reviewers assessed study quality.

Data extraction
Data were extracted on recurrence rates and used to calculate mean differences between intervention and control groups, together with 95% confidence intervals (CI). Data were extracted on a per-protocol basis where withdrawals were reported or using an intention-to-treat method where no reasons for withdrawal or description of recurrence were reported. Where recurrence rates were reported as percentage only, the number of patients with recurrence was calculated from the total number of patients.

The authors did not state how many reviewers extracted data.

Methods of synthesis
Pooled weighted mean differences (WMD) were calculated if at least two studies reported the same endpoint. Pooled analysis was conducted using a fixed-effect model (statistical heterogeneity absent) or a random-effects model (significant statistical heterogeneity).

Results of the review
Twenty-five studies were included in the analysis. The number of participants was not reported. Eighteen studies reported adequate sequence generation. Fifteen studies reported adequate concealment of allocation. Twenty-one studies reported blinding. Twenty-four studies addressed incomplete outcome data and freedom from selective reporting.
Mesalamine: Compared to placebo, mesalamine was significantly more effective in preventing clinical recurrence of Crohn’s disease (WMD 8.8%, 95% CI 2.0 to 15.7%; four studies; no significant heterogeneity). There were no significant differences between mesalamine and placebo for endoscopic recurrence (five studies; evidence of statistical heterogeneity p<0.001). Surgical recurrence was not evaluated in controlled studies.

Metronidazole/ornidazole: Compared with placebo, nitroimidazolic antibiotics were more effective in preventing postoperative clinical recurrence of Crohn’s disease at one year follow-up (WMD 24.2%, 95% CI 11.6% to 36.9%; two studies) but there were no significant differences between groups at three-year follow-up. Endoscopic recurrence was significantly reduced at three-month follow-up for nitroimidazolic antibiotics compared with placebo (WMD 23.7%, 95% CI 6.4% to 41.4%; two studies). There was no evidence of statistical heterogeneity for these analyses.

Thiopurines: At one-year follow-up there were no significant differences between thiopurines and placebo or mesalamine for clinical recurrence of Crohn's disease (four studies). At two-year follow-up thiopurines were significantly more effective than placebo or mesalamine for clinical recurrence (WMD 13.1%, 95% CI 2.3% to 23.9%; two studies). Endoscopic recurrence rates were significantly reduced at one year in the thiopurine group compared to placebo (WMD 19.7, 95% CI 8.4% to 31%; three studies). There was no evidence of statistical heterogeneity for these analyses.

Infliximab: One study with 24 patients reported that infliximab had significantly lower endoscopic recurrence rates (9.1%) than placebo (84.5%) at one year.

Compared to placebo, buodenoside, probiotics, interleukin-10 or any surgical procedure did not generally demonstrate any significant difference in postoperative recurrence rates (where reported) in Crohn’s disease.

Results for individual studies were reported.

Authors' conclusions
Among the different drug regimens and surgical techniques only thiopurines and nitroimidazolic antibiotics were able to reduce postoperative clinical as well as endoscopic recurrence of Crohn’s disease. Mesalamine seemed superior to placebo in preventing clinical recurrence. Infliximab seemed superior to placebo in preventing endoscopic recurrence.

CRD commentary
The review question was clear with broadly defined inclusion criteria. Relevant sources were searched. No attempts were made to locate unpublished studies and the limitation to studies in English meant there was potential for publication and language biases. It was not reported whether appropriate methods to reduce reviewer error and bias were used during the review process. Study quality was assessed and results of the assessment for individual studies were reported. Study characteristics were not reported for individual studies so the generalisability of the results was unclear. The number of participants in each study was not reported so it was unclear whether studies were adequately powered to detect a difference between groups. Studies were combined in a meta-analysis where possible but methods to assess statistical heterogeneity were not reported. The authors stated that there were variations in inclusion and exclusion criteria, definitions of recurrence and length of follow-up that may have affected the results.

The authors’ conclusions reflect the evidence presented but lack of detail of the included studies, variation between studies and lack of reporting of review methods make the reliability of the conclusions unclear.

Implications of the review for practice and research
Practice: The authors stated a number of recommendations for treatment (details reported in the review). Clinicians must outweigh the risk of each postoperative treatment against numbers needed to treat to prevent a single recurrence.

Research: The authors stated a need for large controlled trials with long-term follow-up to study how the different regimens affect or prevent surgical recurrence of Crohn’s disease.

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