Meta-analysis: combination endoscopic and drug therapy to prevent variceal rebleeding in cirrhosis

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CRD summary
This review aimed to determine whether, in patients with cirrhosis, combined endoscopic and drug therapy prevents re-bleeding and improves survival more than either therapy alone. The authors concluded that combination therapy is the better treatment for the prevention of re-bleeding. The authors’ conclusions reflect the evidence presented and are likely to be reliable.

Authors' objectives
To determine whether, in patients with cirrhosis, combined endoscopic and drug therapy prevents re-bleeding and improves survival more than either therapy alone.

Searching
MEDLINE, EMBASE, the Cochrane CENTRAL Register and the Cochrane Database of Systematic Reviews were searched from 1980 to 2007; the search terms were reported. The reference lists of relevant articles were screened. Abstracts presented at meetings of the American Gastroenterological Association, the American Association for the Study of Liver Diseases, the European Association for the Study of the Liver, the American Society of Gastrointestinal Endoscopy and the British Society of Gastroenterology were searched manually (also from 1980 to 2007). The trial registries Current Controlled Trials and ClinicalTrials.gov were also searched. There were no language restrictions.

Study selection
Randomised controlled trials (RCTs) of patients with cirrhosis and a previous episode of oesophageal variceal haemorrhage were eligible for inclusion in the study. Trials also had to compare the combination of endoscopic therapy (injection sclerotherapy or band ligation) and drug therapy (non-selective β-adrenergic blockers) with endoscopic or β-blocker therapy alone, and had to use one (or more) re-bleeding or variceal re-bleeding events, or all-cause mortality, as an outcome.

Of the studies included, propranolol (15 trials) or nadolol (8 trials) was used as the drug therapy. Seventeen studies used sclerotherapy and six used band ligation as endoscopic therapy; as a comparator, 18 used endoscopic therapy and five drug therapy. In 12 trials the first session of endoscopic therapy was carried out during emergency endoscopy. The mean participant age was 53 years and 75% of the participants were male. Alcohol was the cause of liver disease in around half of the participants.

Two reviewers independently selected studies for inclusion.

Assessment of study quality
Trial quality was assessed using a modified established standard, based on generation of allocation sequence, allocation concealment, efficacy of randomisation, investigator blindness, adherence of analysis to the intention-to-treat principle, and descriptions of withdrawals and drop-outs. Where necessary, original investigators were contacted for further data.

Two reviewers assessed trial quality, with any disagreements resolved by discussion with a third reviewer.

Data extraction
Data on the number of outcomes in the intervention and comparator groups were extracted. Risk ratios (RRs) for re-bleeding events and Peto odds ratios (ORs) for mortality were then calculated, along with 95% confidence intervals (CIs).
Two reviewers extracted the data, with any disagreements resolved by discussion with a third reviewer.

**Methods of synthesis**
Meta-analyses were performed using a fixed-effect model (when statistical heterogeneity was not significant) or a random-effects model (when heterogeneity was present). The studies were weighted, but the method of weighting was not stated. Meta-regressions and stratified meta-analyses were carried out to explore the influence of study characteristics and clinical variables on treatment effect.

Heterogeneity between the trials was investigated using the Cochran Q test and the $I^2$ statistic. Publication bias was investigated using funnel plots and Egger's test.

**Results of the review**
Twenty-three RCTs (n=1,860) were included in the review. The sample sizes ranged from 28 to 171 participants.

Of the 16 trials published as articles, half fulfilled more than four of the six quality measures, but none met all of them. The investigator was blinded in only 2 trials. The baseline characteristics of the treatment and control groups were balanced in all trials. The median follow-up periods of trials comparing combination therapy with endoscopic therapy and with drug therapy were 18.7 and 24 months, respectively. Publication bias was observed for re-bleeding, but not for mortality.

Combination therapy was more effective than endoscopic therapy at reducing re-bleeding (RR 0.68, 95% CI: 0.52, 0.89) and mortality (Peto OR 0.78, 95% CI: 0.58, 1.07), although the mortality result was not statistically significant. Substantial clinical and statistical heterogeneity was found for re-bleeding ($I^2=61\%$; $p<0.001$), but not for mortality ($I^2=0\%$; $p=0.85$). In the meta-regression analyses, no covariate was related to treatment effect for re-bleeding; for mortality, trials with longer follow-up showed an effect size close to that observed in the overall analysis, whereas trials with shorter follow-up did not show any effect. Combination therapy seemed to reduce the mortality rate in trials with intention-to-treat designs.

Combination therapy was more effective than drug therapy for preventing re-bleeding (RR 0.71, 95% CI: 0.59, 0.86) and mortality (Peto OR 0.70, 95% CI: 0.46, 1.06), although the mortality result was not statistically significant. No significant heterogeneity was found.

Combination therapy also reduced variceal re-bleeding and variceal recurrence. Asthenia was the most commonly reported β-blocker-related side-effect. Further analyses were reported.

**Authors' conclusions**
A combination of endoscopic and drug therapy is better than either treatment alone in the prevention of overall and variceal re-bleeding in patients with cirrhosis and an initial variceal bleeding event.

**CRD commentary**
This review addressed a clear question and was supported by appropriate inclusion criteria. Attempts to identify all relevant studies were undertaken by searching electronic databases and other sources, including conference abstracts. Study validity was adequately assessed and was used in interpreting the analyses. Comprehensive details of the studies were provided, and appropriate methods were used to pool the results and to investigate statistical heterogeneity. However, the method of weighting used and the p-values associated with effect sizes were not reported. This was generally a well-conducted review, and the authors' conclusions reflect the evidence presented and are likely to be reliable.

**Implications of the review for practice and research**
Practice: The authors stated that a combination of endoscopic and drug therapy is appropriate for the secondary prevention of re-bleeding in patients with cirrhosis and an initial oesophageal variceal bleeding event.

Research: The authors stated that further studies are needed to define subgroups of patients more likely to benefit from
combination therapy.

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