Combined ligation and sclerotherapy versus ligation alone for secondary prophylaxis of esophageal variceal bleeding: a meta-analysis
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Authors' objectives
To incorporate the most recent data from clinical trials comparing ligation with and without sclerotherapy in achieving rapid and complete eradication of oesophageal varices, in order to resolve discrepancies among previous reviews, and to obtain precise estimates of clinically important treatment outcomes.

Searching
MEDLINE was searched from 1992 to 2000. The search strategy utilised the following MeSH terms and keywords alone and in combination: 'variceal bleeding', 'portal hypotension', 'sclerotherapy', 'band', 'ligation', 'endoscopy' and 'clinical trial'. In addition, the reference lists of the identified studies were reviewed and abstracts from conference proceedings were scanned.

Study selection
Study designs of evaluations included in the review
Only randomised controlled trials (RCTs) were eligible for inclusion.

Specific interventions included in the review
Studies comparing endoscopic variceal ligation (EVL) and variceal ligation plus sclerotherapy (EVSL), aimed at obliterating oesophageal varices, were eligible for inclusion. Ligation was performed using an endoscopic ligating device, and the number of ligating bands ranged from 8 to 12 per treatment session. In patients receiving the combination therapy, the sclerosant was injected after each ligation was placed. Primary sclerosants used in the included studies were: sodium tetradecyl sulfate (1.5%) combined with alcohol or 50% dextrose; and ethanolamine (5%)-polidocconol (1%). All treatment sessions were conducted at intervals of 1 to 3 weeks.

Participants included in the review
Studies that included patients who had bled from varices before entering the study were eligible for inclusion. The mean age ranged from 38 to 55 years. The proportion of patients with cirrhosis ranged from 80 to 97%.

Outcomes assessed in the review
The major outcomes of interest were oesophageal variceal bleeding, mortality rates, and the number of treatment sessions to obliteration. Other outcomes included in the review were bleeding complication secondary to treatment-related oesophageal ulcer, oesophageal stricture, and pneumonia.

How were decisions on the relevance of primary studies made?
Two investigators independently evaluated the studies for possible inclusion and subsequently resolved any disagreements by discussion. The investigators were blinded to the journal, author and institution.

Assessment of study quality
The methodological quality of the included studies was assessed using a modified published checklist (see Other Publications of Related Interest no.1). The studies were assessed using the following four criteria: proper generation of the treatment allocation sequence; intention to treat analysis; double-blinding; and patients lost to follow-up.

An overall quality score out of a maximum of 15 was assigned to each study. The criteria were modified for trials involving variceal rebleeding. One investigator extracted data on the four quality criteria from the included studies. Two investigators independently assigned an overall quality score for the trials. Any differences were resolved by consensus.
Data extraction
Two investigators independently extracted data on all the outcomes. The data were extracted into tables under the following headings: the number of patients; age; sex; Child Class; the number of patients with cirrhosis; the number of patients who drank alcohol; the number of patients with noncirrhotic portal hypertension; varices grade; the number of patients with variceal bleeding; the number of deaths; the number of patients with obliteration; the mean treatment sessions to obliteration; and adverse events.

Methods of synthesis
How were the studies combined?
The odds ratio (OR) was calculated for each outcome. Fixed-effect and random-effects models (see Other Publications of Related Interest nos.2-3, respectively) were used to estimate the summary treatment effect for all studies combined. To check for possible publication bias, the authors created inverted funnel plots of individual study results plotted against sample size (see Other Publications of Related Interest no.4). To identify any studies that exerted a disproportionate influence on the summary treatment effect, the authors deleted individual studies one at a time.

How were differences between studies investigated?
The Mantel-Haenszel test for statistical heterogeneity (see Other Publications of Related Interest no.5) was used to assess the validity of combining results. Sensitivity analyses were conducted for each of the three major outcomes. To assess the robustness of the findings over time, the authors ordered studies by year of publication and performed a cumulative meta-analysis (see Other Publications of Related Interest no.1). To explore the influence of study level factors on the treatment effect, the authors used a series of log-linear models, each fitted by maximum likelihood estimation. The goodness of fit of these models was compared using an analysis of deviance, a likelihood ratio test analogous to analysis of variance (see Other Publications of Related Interest no.6).

Results of the review
Seven RCTs (n=445) were eligible for inclusion.

The methodological quality score of the seven RCTs ranged from 6 to 11.5 out of a maximum score of 15. The allocation sequence was judged as not properly concealed in all seven studies.

Variceal bleeding: 4 studies (n=57) compared the efficacy of EVL and EVSL in achieving haemostasis in actively bleeding varices. On pooled analysis, haemostasis for active bleeding was similar for EVL and EVSL (OR 1.01, 95% confidence interval, CI: 0.43, 2.36). Seven studies (n=445) compared the effectiveness of EVL and EVSL in reducing variceal bleeding rate. The combined data analysis showed rebleeding to be similar in both treatment groups (OR 1.12, 95% CI: 0.69, 1.81).

Death: mortality did not significantly differ between patients treated with EVL and those treated with EVSL (OR 1.1, 95% CI: 0.7, 1.74) in 7 studies (n=445). There was no statistical heterogeneity for the analysis of deaths owing to rebleeding (p=0.45).

Variceal obliteration: the pooled analysis from 7 studies (n=445) showed significantly lower variceal obliteration in the EVL group than in the EVSL group (fixed-effect OR 0.57, 95% CI: 0.37, 0.87). The heterogeneity test was significant (p=0.02) and the random-effects model failed to show statistical significance (random-effects OR 0.56, 95% CI: 0.26, 1.2).

Adverse events: the data combined from 7 studies (n=442) using both fixed-effect and random-effects models showed significantly higher adverse events with the EVSL group (OR 0.37, 95% CI: 0.21, 0.62). The difference was due to a significantly higher incidence of oesophageal stricture in the EVSL group (OR 0.07, 95% CI: 0.01, 0.31). The data on bleeding from treatment-induced ulcers, episodes of pulmonary infection, and spontaneous bacterial peritonitis were similar in both groups.

Separate subgroup analyses for rebleeding and mortality were carried out in relation to the methodological quality score, the proportion of patients with alcoholic cirrhosis, and the proportion of patients with Child-Pugh classification C cirrhosis. These had similar results to those of the main meta-analysis.
Authors' conclusions
The combination of ligation and sclerotherapy offered no advantage over ligation alone in the prevention of rebleeding and in the reduction of mortality. It was also associated with a higher complication rate of oesophageal stricture.

CRD commentary
The methodological quality of this review was good. The authors set out a clear objective and reported detailed inclusion criteria. The search carried out by the authors was adequate although they could have searched additional sources for studies. It is also unclear why studies published prior to 1992 were not searched for. Searching only one database increases the likelihood that studies were missed. The authors reported that they explored publication bias but the results were not presented. The process of, and the number of reviewers who carried out the study selection and data extraction were reported. The methodological quality of the included studies was assessed using a published checklist. Study details were well presented in tables. The method of pooling was appropriate but the authors did not adequately investigate heterogeneity: where heterogeneity existed, the results were simply presented in a random-effects model and were not investigated. The authors' conclusions follow on from the results given the limitations outlined, but additional sources should have been searched.

Implications of the review for practice and research
Practice: The authors state that because combined ligation and sclerotherapy lengthens the time required for treatment without improving efficacy, it cannot be recommended in actively bleeding varices.

Research: The authors did not state any implications for further research.

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Other publications of related interest

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Record Status
This is a critical abstract of a systematic review that meets the criteria for inclusion on DARE. Each critical abstract contains a brief summary of the review methods, results and conclusions followed by a detailed critical assessment on the reliability of the review and the conclusions drawn.