A meta-analysis of endoscopic variceal ligation for primary prophylaxis of esophageal variceal bleeding

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Authors' objectives
To compare the effect of ligation with 'no treatment' and treatment with beta-blockers, on the risks of first episode of variceal bleeding, bleed-related mortality, and all-cause mortality.

Searching
MEDLINE and EMBASE were searched from 1995 to 1999 using the terms 'variceal near 1 ligation', 'esophageal varices' and 'primary'. The Cochrane Controlled Trials Register was searched using the terms 'variceal' and 'ligation'. Sources containing abstracts from national meetings held between 1997 and 1999 were searched manually for the following organisations: the American Gastrointestinal Association; the American Society for Gastrointestinal Endoscopy; the American Association for the Study of Liver Disease; the European Association for the Study of Liver; and the American College of Gastroenterology. This was achieved by examining indexes for abstracts using the terms 'esophageal' and 'ligation'. Finally, the bibliographies from retrieved reports were scanned.

Study selection
Study designs of evaluations included in the review
Randomised controlled trials (RCTs) were eligible. Review articles, editorials and correspondence were excluded. The duration of follow-up ranged from 12 to 32 months.

Specific interventions included in the review
Comparisons of endoscopic ligation with no treatment, placebo, or non-selective beta-adrenergic blockade, were eligible. Comparisons with nitrates and sclerotherapy were excluded. In 6 studies, ligation was performed every 1 to 3 weeks until the varices were obliterated. The methods of ligation varied among 5 published trials, with the most common method involving the placement of bands on varices within the distal 5 cm of the oesophagus. The number of bands used varied from 1 or 2, to as many as possible, per session. In one study, sucralfate granules were administered to all patients until the varices were eradicated. The daily dose of propranolol in 3 trials ranged from 40 to 120 mg (mean 70 to 73 mg).

Participants included in the review
Patients with oesophageal varices and no prior episode of variceal or upper gastrointestinal tract haemorrhage were eligible. The mean age of the patients was 48 years and 76% of them were male (based on 6 trials). Between 91 and 100% of the patients had cirrhosis; on average, this was ethanol-related in 29% of them (based on 7 trials). Some trials provided information on Child class; the mean percentages were 27% (range: 18 to 37) for Child class A, 45% (range: 36 to 52) for class B, and 28% (range: 13 to 38) for class C. Most patients had large varices, i.e. grade III and IV, or Japanese classification F3.

Outcomes assessed in the review
Studies that assessed at least one of the following outcomes were eligible: first episode of variceal bleeding, bleed-related mortality, and all-cause mortality. Adverse effects were also discussed in the review.

How were decisions on the relevance of primary studies made?
The two investigators independently rated trial quality and any discrepancies were resolved by discussion.

Assessment of study quality
The validity of those studies published in full was assessed and scored on the following criteria:

- clearly specified inclusion criteria;
clearly specified exclusion criteria;

concealment of allocation;

baseline equivalence of within-trial treatment groups, defined as no statistically-significant differences for well-established prognostic variables and clinical differences of 25% or less;

investigator blinded;

comparable interventions within-trial treatment groups; and

completeness of follow-up, defined as a greater than 90% follow-up with no preferential loss to follow-up.

One point was awarded for each satisfied criterion giving a maximum possible score of 7 points. The two investigators independently applied the inclusion and exclusion criteria.

**Data extraction**

The two investigators independently extracted descriptive and clinical data from the studies, including the number of patients per treatment arm and outcomes. Any discrepancies were resolved by discussion. The following information was tabulated for those studies published in full: author and year of publication; inclusion criteria; exclusion criteria; details of interventions; details of cointerventions; follow-up frequency for each treatment arm; outcomes; and time to follow-up.

**Methods of synthesis**

How were the studies combined?

A pooled relative risk (RR), along with the 95% confidence intervals (CIs), was calculated for each outcome using a random-effects model (see Other Publications of Related Interest no.1-2). The point estimates for the effect of treatment were calculated using weighted averages of stratum-specific RR; these were weighted primarily using the reciprocals of the variance, and secondarily from a correction factor reflecting the degree of statistical heterogeneity (see Other Publications of Related Interest no.3). The number-needed-to-treat (NNT) and 95% CI were also calculated for those RRs demonstrating a clear benefit for one treatment.

Publication bias was assessed using the 'file drawer effect'. It was estimated that 10 unpublished studies would be required to nullify the results for the comparison between ligation and placebo for the outcome of first variceal bleed.

How were differences between studies investigated?

Sources of clinical heterogeneity were described, and statistical heterogeneity was assessed using the method of DerSimonian and Laird (see Other Publications of Related Interest no.4). Results from the studies published in full were compared with results from abstracts. In addition, the results were reanalysed after including three studies published in abstract form after completion of the review.

**Results of the review**

Nine RCTs (n=884) were included, of which 5 were published in full.

The 5 trials published in full were of comparable methodological quality (all scored 5 points). The treatment and baseline groups were comparable at baseline, the groups received comparable follow-up, and the analysis was performed on an intention to treat basis. The exclusion and inclusion criteria were consistent, and 4 of the 5 studies provided endoscopically-based definitions for oesophageal variceal bleeding.

Ligation versus no treatment (5 RCTs, 601 patients).

There was no evidence of heterogeneity among studies for any of the outcomes.
Ligation significantly reduced the risk for a first episode of variceal bleeding. The absolute risk was reduced from 18 to 4% for a RR of 0.36 (95% CI: 0.26, 0.50). The NNT was 4 (95% CI: 3, 6).

Ligation also significantly reduced the risks for upper gastrointestinal bleed-related mortality and all-cause mortality. For upper gastrointestinal bleed-related mortality, the RR was 0.20 (95% CI: 0.11, 0.30) and the NNT was 7 (95% CI: 5, 9). For all-cause mortality, the RR was 0.55 (95% CI: 0.43, 0.71) and the NNT was 5 (95% CI: 4,9).

Ligation versus beta-blockers (4 RCTs, 283 patients).

Ligation significantly reduced the risk for a first episode of variceal bleeding. The absolute risk was reduced from 15.7 to 7.6% for a RR of 0.48 (95% CI: 0.24, 0.96). The NNT was 13 (95% CI: 6, 158).

For bleed-related mortality, there was no difference between the treatment groups (RR 0.61, 95% CI: 0.20, 1.88). However, for all-cause mortality (3 trials), the risk was 17% in the ligation group and 19% in the beta-blocker group (RR 0.95, 95% CI: 0.56, 1.62).

Comparison of results from 3 fully published papers and 2 abstracts.

For first variceal bleed, the RRs were 0.36 for published studies and 0.37 for abstracts, with NNTs of 4 and 5, respectively.

For bleed-related mortality, the RRs were 0.25 (95% CI: 0.10, 0.59) for published studies and 0.17 for abstracts of 0.17 (95% CI: 0.37, 0.43), with NNTs of 9 and 6, respectively.

For all-cause mortality, comparable RRs and NNTs were found for published studies and abstracts (RRs were 0.55 and 0.56, respectively, with NNTs of 5 and 6).

The inclusion of interim data from ongoing studies had a negligible effect on results.

Adverse effects.

The details on adverse effects varied among the published studies. The abstracts contained little information about adverse effects.

One study using propranolol reported adverse reactions to the drug in 35% of the patients, but only 2 patients withdrew. One abstract reported that 24 out of 66 patients withdrew from the propranolol arm due to adverse effects. Oesophageal ulcers were common in patients undergoing ligation but adverse effects were rare. The most common symptoms (lasting 24 to 48 hours) were chest pain, dysphagia, and low-grade fever.

Authors' conclusions

Compared with untreated controls, prophylactic ligation reduced the risks of variceal bleeding and mortality. Compared with beta-blockers, ligation reduced the risk for first variceal bleed but had no effect on mortality.

CRD commentary

The aims were stated and the inclusion criteria were defined in terms of study design, interventions, participants and outcomes. Several relevant sources were searched and the keywords used were reported. In addition, attempts were made to locate unpublished material and publication bias was assessed. The methods used to select the studies were described. Validity was assessed and scored using defined criteria, and the methods used to assess the validity were reported. Relevant data were presented in tabular format, and details were given of the methods used to extract the data.

Clinical heterogeneity among studies was discussed and statistical heterogeneity was assessed. A meta-analysis was appropriate given the evidence of clinical and statistical homogeneity. The results from abstracts and studies published in full were compared. However, there was a discrepancy in the results reported for bleed-related mortality: the reported RR for abstracts (0.17) appears to be in error since it lies outside of the confidence range.
The evidence presented supports the authors’ conclusion.

**Implications of the review for practice and research**
Practice: The authors state that prophylactic ligation should be considered for patients with large oesophageal varices who cannot tolerate beta-blockers.

Research: The authors state that further research should compare ligation and beta-blockers to determine their effect on mortality, and to measure the cost-effectiveness of ligation.

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