Endoscopic ligation compared with sclerotherapy for treatment of esophageal variceal bleeding: a meta-analysis

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Authors' objectives
To compare the effects of endoscopic ligation with those of endoscopic sclerotherapy in the treatment of patients with bleeding oesophageal varices.

Searching
Searches were made of MEDLINE, from 1983 (keywords given) and Scisearch, for published studies. Searches were also made of the Federal Research in Progress, NTIS, Conference Papers Index, Biosis Previews for unpublished data. Meeting abstracts of the American Gastrointestinal Association from 1988 to May 1994 were also examined. Manufacturers of the ligation device and investigators in the field were contacted.

Study selection
Study designs of evaluations included in the review
Randomised controlled trials (RCTs) were included.

Specific interventions included in the review
Intravariceal injections (using Bard Interventional Products);
Sclerosing agents: Sodium Tetradecyl sulfate (n=5), combined with 33% alcohol and saline, or with 25% dextrose (n=1). Ethanolamine (5%) or Polidocanol (1%).

Participants included in the review
Five hundred and forty-seven patients presenting with bleeding oesophageal varices (mean age range 46-56 years); patients with cirrhosis; patients with alcoholic cirrhosis; patients with Child C liver disease.

Outcomes assessed in the review
Haemostasis for active bleeding, rebleeding due to varices, mortality caused by bleeding, complications, variceal obliteration. (Complications included oesophageal stricture, bleeding due to ulcers caused by treatment, pulmonary infection, bacterial peritonitis, complications leading to death).

How were decisions on the relevance of primary studies made?
The two authors independently reviewed titles and abstracts of all the studies, and retrieved all articles meeting the inclusion criteria. This exercise was repeated with the full text of articles. The kappa statistic was calculated for inter-rater reliability.

Assessment of study quality
Studies included had to be:

1. Randomised comparisons of endoscopic ligation and sclerotherapy.
2. Have a target population composed of patients with esophageal variceal bleeding.
3. Outcome measures including either rebleeding, mortality, complications, or treatment sessions to obliteration.

Relevant studies were assessed for methodological quality. Each study was scored based on specifications of the population (patient selection, patient characteristics, definition of bleeding at entry), intervention (randomisation, blinding, endoscopic treatment) and outcome measure (definition of rebleeding, rebleeding site diagnosis). The two
authors independently assessed methodological quality and any disagreement was resolved by consensus. The kappa statistic was calculated for inter-rater reliability.

**Data extraction**
The two authors independently extracted the data from each study. A copy of the completed data abstraction form was sent to the authors of each study who were asked to correct any erroneous assessments and provide missing information. Authors of abstracts were asked to provide full information about methods and results.

**Methods of synthesis**
How were the studies combined?
For each of the outcome measures, the studies were combined in a meta-analysis by a pooled odds ratio (OR), using a modified version of the Mantel-Haenszel technique.

How were differences between studies investigated?
The Breslow-Day method was used to test for homogeneity across studies.

Subgroup analysis was conducted: Studies scoring 8 or more on the quality assessment exercise were compared to those scoring less than 8.

Studies in which at least 75% of the patients had alcoholic cirrhosis (AC) were compared to those studies with fewer than 75% of AC patients.

Studies in which at least 40% of patients has Child C liver Disease (CCLD) were compared to those studies with fewer than 40% CCLD patients.

Abstracts of papers were compared to studies published in full.

**Results of the review**
Seven RCTs were included in the review (547 patients).

5 studies included patients with active bleeding and information on haemostasis (106 patients).

5 studies provided information on mortality due to bleeding.

Evidence of statistical heterogeneity was not found (p>0.55 for all analyses).

For patients with actively bleeding varices the haemostasis rates were similar after ligation and sclerotherapy (OR 1.14, 95% confidence interval, CI: 0.44, 2.90).

Rebleeding was less common with ligation therapy compared to sclerotherapy (OR 0.52, 95% CI: 0.37, 0.74), the mortality rate (OR 0.67, 95% CI: 0.46, 0.98), and the rate of death due to bleeding (OR 0.49, 95% CI: 0.24, 0.996).

The rate of rebleeding due to varices was lower in patients receiving ligation (OR 0.47, 95% CI: 0.29, 0.78], as was the rate of rebleeding due to treatment-induced ulcers (OR 0.56, 95% CI: 0.28, 1.15, p=0.16).

Death not due to bleeding was also less frequent in the ligation group (OR 0.62, 95% CI: 0.35, 1.07, p=0.11).

No significant differences in the proportion of pulmonary infections or episodes of spontaneous bacterial infections were found between the two approaches.

Deaths due to complications occurred in 2 of the 210 patients treated with ligation, compared with 7 of the 211 receiving sclerotherapy (OR 0.47, 95% CI: 0.15, 1.48, p=0.30).
Variceal obliteration was achieved in similar proportions for both treatments (OR 1.24, 95% CI: 0.87, 1.67); the proportion ranged from 27 to 90%. There were 2.2 (CI, 0.09 to 0.35) fewer treatment sessions needed to achieve variceal obliteration with ligation than with sclerotherapy.

Cost information
Six of the seven studies suggested that one to three fewer endoscopic treatment sessions would be required to achieve variceal obliteration with ligation. The costs of the equipment for either ligation or sclerotherapy are similar.

Authors' conclusions
On the basis of lower rates of rebleeding, mortality and complications and the need for fewer endoscopic treatments, ligation should be considered the endoscopic treatment of choice for patients with oesophageal variceal bleeding. However, further large-scale RCTs with longer follow-up and economic evaluation would be useful to firmly establish the utility of ligation therapy, compared with sclerotherapy.

CRD commentary
This is a very comprehensive overview, with a thorough search strategy and clearly-defined reviewing procedure. The limitations of the scoring system employed in the review are highlighted by the lack of significant differences between the findings of high and low scoring studies.

While the quality assessment procedure includes important methodological issues, length of follow-up (only three studies provide details of follow-up), controlling for confounders and attrition rates (two studies do not provide details of attrition) are not considered.

Implications of the review for practice and research
On the basis of current evidence, ligation should be considered the endoscopic treatment for patients with oesophageal variceal bleeding.

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