Pharmacotherapy plus endoscopic intervention is more effective than pharmacotherapy or endoscopy alone in the secondary prevention of esophageal variceal bleeding: a meta-analysis of randomized, controlled trials

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CRD summary
The authors concluded that pharmacotherapy might be as effective as endoscopy in reducing re-bleeding rates and all-cause mortality in gastro-oesophageal bleeding. Pharmacotherapy plus endoscopy was more effective than endoscopy alone. Combined treatment was more effective in only two of four outcomes measured and incomplete reporting of the review methods and trial quality mean that these conclusions may not be reliable.

Authors' objectives
To compare pharmacotherapy with endoscopic procedures for oesophageal variceal bleeding.

Searching
PubMed, EMBASE and the Cochrane Central Register of Controlled Trials (CENTRAL) were searched up to November 2006, using reported search terms. Abstracts and reference lists of published articles were also screened.

Study selection
Randomised controlled trials (RCTs) were eligible if they compared pharmacotherapy with or without sclerotherapy versus sclerotherapy alone or compared pharmacotherapy with or without ligation versus ligation alone in adults (aged over 16 years) with at least one previous episode of gastro-oesophageal bleeding. Trials of interventions for the primary prevention of gastro-oesophageal bleeding and those that only included patients with gastric varices were excluded. Trials had to assess overall mortality, mortality due to gastro-oesophageal bleeding, recurrence of bleeding, or recurrence of bleeding from oesophageal varices. The review compared pharmacotherapy with endoscopic procedures (defined as sclerotherapy or band ligation).

In most of the included trials, pharmacotherapy was with beta-blockers (mostly propranolol, with a few trials using nadolol with or without nitrates); one trial used sucralfate. Where reported, the sclerosants included aethoxysclerol, polidocanol, and ethanolamine. In most of the trials the mean interval between endoscopic sessions was seven to 14 days. Patients had Child-Pugh scores from A to C; some trials were only in patients with scores of B and C, or A and B. In most of the trials patients had cirrhosis due to alcoholism or viral infection. Trials used different definitions of re-bleeding and variceal bleeding, and the details were reported. The mean age of patients ranged from 34 to 64 years and most of them were male.

The authors did not state how papers were selected for the review, nor how many reviewers performed the selection.

Assessment of study quality
The authors did not state that they assessed validity.

Data extraction
For each trial, the number of patients with outcomes of interest was presented, together with relative risks and 95% confidence intervals.

Two reviewers independently extracted outcome data and resolved disagreements by discussion.

Methods of synthesis
Pooled relative risks and 95% confidence intervals were calculated using the Mantel-Haenszel fixed-effect model in the absence of heterogeneity and a random-effects model in its presence. Heterogeneity was assessed using the Cochran Q statistic. Differences between trials were discussed and funnel plots were used to assess publication bias.
**Results of the review**
The review text stated that 26 RCTs were eligible for meta-analysis, but the review abstract stated that 25 trials with 2,159 patients were eligible. Details of 26 trials were presented in tables. There was no evidence of publication bias.

**Pharmacotherapy versus endoscopic procedures** (12 RCTs, n=1,252 patients): There was no statistically significant difference between pharmacotherapy and endoscopic therapy in re-bleeding, variceal re-bleeding, all-cause mortality, or mortality due to re-bleeding. Significant heterogeneity was found for re-bleeding (p=0.001) and re-bleeding due to varices (p=0.001).

**Pharmacotherapy plus endoscopic procedure versus endoscopic procedure alone** (reported on different occasions as 13 and 14 RCTs, n=1,069 patients): Pharmacotherapy plus endoscopic procedure was associated with a statistically significant reduction in re-bleeding (RR 0.62, 95% CI 0.52 to 0.74) and variceal re-bleeding (RR 0.60, 95% CI 0.44 to 0.82) compared with endoscopy alone. There was no statistically significant difference between endoscopic procedures with versus without pharmacotherapy, in all-cause mortality nor mortality due to re-bleeding. No significant heterogeneity was found for any of these analyses.

**Authors' conclusions**
Pharmacotherapy might be as effective as endoscopic therapy in reducing re-bleeding rates and all-cause mortality in patients with gastro-oesophageal bleeding. Pharmacotherapy plus endoscopic procedures was more effective than endoscopic procedures alone.

**CRD commentary**
The review question was clearly stated and the inclusion criteria were appropriately defined. Several relevant sources were searched, but no attempts to search for unpublished trials were reported. Formal assessment showed no evidence of publication bias. Methods were used to minimise reviewer errors and bias in the extraction of data, but it was not clear whether similar steps were taken in the trial selection. Only RCTs were included, but trial validity was not assessed and so the results from these RCTs and any synthesis might not be reliable. Appropriate methods were used in the meta-analyses, heterogeneity was assessed, and forest plots were presented. The authors acknowledged the differences between trials with respect to populations, treatment protocols, and definitions of re-bleeding. There were discrepancies in the reporting of the number of included trials (see Results section).

The authors’ conclusions were largely supported by the evidence. The fact that no difference was found between pharmacotherapy and endoscopic procedures did not rule out this possibility, but the benefits of the combined therapy compared with endoscopic procedures alone relied upon evidence from only two of the four outcomes measured. The incomplete reporting of the review methods and the lack of assessment of trial quality make it difficult to judge the reliability of the authors' conclusions.

**Implications of the review for practice and research**
The authors did not state any implications for practice nor research.

**Funding**
No funding received.

**Bibliographic details**

**PubMedID**
19643407

**DOI**
10.1016/j.gie.2009.02.029
Original Paper URL
http://www.giejournal.org/article/S0016-5107(09)00428-3/abstract

Indexing Status
Subject indexing assigned by NLM

MeSH
Adrenergic beta-Antagonists /therapeutic use; Combined Modality Therapy; Esophageal and Gastric Varices /drug therapy /etiology /mortality /prevention & control; Esophagoscopy; Gastrointestinal Hemorrhage /drug therapy /etiology /mortality /prevention & control; Humans; Ligation; Randomized Controlled Trials as Topic; Recurrence; Risk Factors; Sclerosing Solutions /administration & dosage; Sclerotherapy

AccessionNumber
12009110329

Date bibliographic record published
03/02/2010

Date abstract record published
28/04/2010

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.