Benefit of combination beta-blocker and endoscopic treatment to prevent variceal rebleeding: a meta-analysis
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CRD summary
The authors concluded that combination endoscopic and beta-blocker therapy was more effective (with lower bleeding rates and mortality) than endoscopic treatment alone in the secondary prophylaxis of oesophageal variceal bleeding in patients with portal hypertension. The authors' conclusion reflects the evidence presented, but the variable quality of included trials means that the reliability of this conclusion is unclear.

Authors' objectives
To compare the effectiveness of combined beta-blocker and endoscopic treatments with endoscopic treatments alone to prevent variceal re-bleeding in patients with portal hypertension.

Searching
MEDLINE and Web of Science were searched for peer-reviewed articles, abstracts, or letters to the editor, from 1900 to April 2010. Search terms were reported. Reference lists were screened. Conference abstracts from various international meetings were searched from 1980 to 2009. There were no language restrictions.

Study selection
Randomised controlled trials (RCTs) that compared combined beta-blocker plus endoscopic treatment (sclerotherapy or banding ligation) versus sclerotherapy or banding ligation alone for the treatment of variceal re-bleeding were eligible for inclusion. Eligible patients had portal hypertension (with or without cirrhosis) and had oesophageal varices previously untreated for bleeding. Beta-blockers had to be given at the start of endoscopic treatment. Trials that associated beta-blockers with nitrates were excluded.

The primary outcomes of interest were all-cause re-bleeding (upper gastrointestinal bleeding of any source), mortality at six, 12, 24 months, and overall re-bleeding and mortality.

Most included trials compared sclerotherapy with combination treatment. The beta-blockers used were propranolol and nadolol. Chronic liver disease was the most common cause of portal hypertension in included trials, mainly due to alcohol abuse. Nearly half of the trials included only patients with cirrhosis. The mean age of participants ranged from 34 to 60 years; men represented over half of participants, ranging from 54 to 90% (where reported).

The authors did not state how many reviewers selected the studies.

Assessment of study quality
Trial quality was assessed with modified criteria from two established sources, and a percentage score was awarded. Additionally, trials were individually assessed for the presence of randomisation, investigator blinding, estimated sample size, and use of intention-to-treat analysis.

Three independent reviewers carried out the quality assessment. Disagreements were resolved by discussion.

Data extraction
Data were extracted to enable the calculation of odds ratios (ORs) and 95% confidence intervals (CIs).

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Methods of synthesis
Odds ratios and 95% confidence intervals were pooled in a fixed-effect meta-analysis. Statistical heterogeneity was
assessed using Breslow-Day's test, and quantified using $I^2$. Where statistical heterogeneity existed, a random-effects meta-analysis (DerSimonian and Laird) was conducted.

Sub-group analyses were carried out separately for trials using sclerotherapy and for trials using banding ligation.

Publication bias was assessed using funnel plots and the Egger test. Further analysis was conducted using trim-and-fill analysis and failsafe calculations.

**Results of the review**
Seventeen RCTs were included in the review (n=1,181 patients). Fourteen trials (n=925 patients) compared sclerotherapy; three trials (n=256 patients) compared banding ligation with combination treatments. Randomisation was appropriately conducted in all trials. Two trials were double-blind (where reported). Less than half of the trials reported estimates of sample size or use of intention-to-treat analysis. Overall follow-up ranged from two to 39 months (mean 15.4 months).

**All-cause re-bleeding**: Variceal re-bleeding rates were significantly lower in the combination treatment groups at six months (OR 1.70, 95% CI 1.24 to 2.34; 11 trials; $I^2=36\%$), 12 months (OR 2.22, 95% CI 1.25 to 3.99; 10 trials; $I^2=62.3\%$, substantial heterogeneity), and overall (OR 2.20, 95% CI 1.69 to 2.85; 16 trials; $I^2=13\%$).

**Mortality**: Mortality was significantly lower in the combination treatment groups at 24 months (OR 1.83, 95% CI 1.16 to 2.90; six trials; $I^2=0\%$) and overall (OR 1.43, 95% CI 1.03 to 1.98; 16 trials; $I^2=0\%$). There were no statistically significant differences between treatment groups at six and 12 months.

**Subgroup analyses**: Subgroup analyses confirmed the main findings for re-bleeding, with combination treatments showing significantly lower overall rates than either of the endoscopic treatments alone (16 trials); substantial heterogeneity was reported for sclerotherapy at 12 months ($I^2=69\%$). There were no statistically significant differences for mortality.

There was no evidence of publication bias in any of the analyses. The authors stated that results for overall re-bleeding were robust, as failsafe numbers were high at all time-points; results for mortality appeared to be less robust.

**Authors' conclusions**
Combination endoscopic and beta-blocker therapy was more effective, with lower bleeding rates and mortality, than endoscopic treatment alone in the secondary prophylaxis of variceal bleeding.

**CRD commentary**
The review question was clear; this was supported by detailed and potentially replicable inclusion criteria. The search strategy appeared to be limited in its inclusion of only two databases, but supplementary searches demonstrated efforts to minimise publication bias. Attempts were also made to minimise language bias. The process for selecting studies was unclear, but other aspects of the review process were conducted with sufficient transparency to minimise error and bias.

Relevant quality assessment criteria were applied to the included trials, indicating that most were not designed to the optimal standard. Trial details were provided. Statistical heterogeneity was assessed. The chosen methods of synthesis were appropriate.

The authors’ conclusion reflects the evidence presented, but the variable quality of the included trials means that the reliability of this conclusion is unclear.

**Implications of the review for practice and research**
**Practice**: The authors stated that (given its widespread use) banding ligation combined with beta-blockers should be the first-line prophylactic treatment of choice in cirrhotic patients who have already experienced bleeding from oesophageal varices.
Research: The authors stated that additional studies with long-term follow-up are needed to confirm the robustness of mortality results from banding ligation trials.

Funding
Not stated.

Bibliographic details

PubMedID
21157975

DOI
10.3748/wjg.v16.i47.5982

Original Paper URL

Indexing Status
Subject indexing assigned by NLM

MeSH
Adrenergic beta-Antagonists /therapeutic use; Adult; Endoscopy /methods; Esophageal and Gastric Varices /pathology /therapy; Gastrointestinal Hemorrhage /prevention & control /therapy; Humans; Ligation; Male; Middle Aged; Randomized Controlled Trials as Topic; Sclerotherapy; Secondary Prevention; Treatment Outcome

AccessionNumber
12011000634

Date bibliographic record published
06/04/2011

Date abstract record published
12/10/2011

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.