Efficacy of beta-adrenergic blocker plus 5-isosorbide mononitrate and endoscopic band ligation for prophylaxis of esophageal variceal rebleeding: a meta-analysis

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CRD summary
The authors concluded that beta-adrenergic blocker plus 5-isosorbide mononitrate was as effective as endoscopic band ligation for the prophylaxis of oesophageal variceal re-bleeding. Evidence appeared to support the authors’ conclusions, but limitations in review methods and analyses based on findings of no significant difference from a few trials weaken the strength of this evidence.

Authors' objectives
To compare the efficacy and safety of beta-adrenergic blocker plus 5-isosorbide mononitrate versus endoscopic band ligation for the prophylaxis of oesophageal variceal re-bleeding.

Searching
MEDLINE, EMBASE, Cochrane Central Register of Controlled Trials (CENTRAL) and China Biological Medicine database were searched, from 1980 to August 2007, for studies published in any language. Search terms were reported.

Study selection
Randomised controlled trials (RCTs) that compared the effects of beta-adrenergic blocker plus 5-isosorbide mononitrate versus endoscopic band ligation for the prophylaxis of oesophageal variceal re-bleeding were eligible for inclusion. Eligible trials were required to assess re-bleeding, all-cause mortality, bleeding-related deaths or complications, and have a minimum duration of follow-up of at least six months.

The beta-blocker in three of the four included trials was nadolol; one trial used propranolol. In one study, some patients in the endoscopic band ligation group underwent simultaneous sclerotherapy. The mean number of endoscopic band ligation sessions ranged from 2 to 3.4. Trials included patients in Child-Pugh classes A, B and C. The mean age of included patients ranged from 51 to 60 years. In all treatment arms, the majority of patients were male.

The authors did not state how papers were selected for the review, or how many reviewers performed the selection.

Assessment of study quality
Two reviewers independently assessed validity using the Jadad score criteria, which included allocation sequence generation, allocation concealment, double-blinding and description of protocol deviations, withdrawals and drop-outs. Trials scoring 3 or more points were considered to be high-quality.

Data extraction
Numbers of patients with outcomes of interest were extracted and used to calculate relative risks (RR) and 95% confidence intervals (CIs).

It appeared that one reviewer extracted data.

Methods of synthesis
Pooled relative risks and 95% confidence intervals were calculated using a fixed-effect method in the absence of significant heterogeneity. Heterogeneity was examined using subgroup analyses. Sensitivity analyses were conducted by using random-effects models. Heterogeneity was assessed using $\chi^2$ and $I^2$ tests.

Results of the review
Four RCTs were included in the review (n=476 patients). Trials scored 5 or 6 points on the Jadad score. The duration of follow-up ranged from approximately eight to 25 months.
There was no statistically significant difference between beta-adrenergic blocker plus 5-isosorbide mononitrate and endoscopic band ligation in rates of re-bleeding (four RCTs, n=476 patients), bleeding-related mortality (three RCTs, n=379 patients), overall mortality (four RCTs, n=476 patients) or complications (four RCTs, n=476 patients). No patients in either group died as a result of complications.

Significant heterogeneity was found for re-bleeding (p=0.01). After exclusion of one trial in which the beta-adrenergic blocker plus 5-isosorbide mononitrate group had a higher percentage of patients with large varices than in the endoscopic band ligation group, heterogeneity was no longer significant (p=0.31) and results were unchanged. No significant heterogeneity was found for the other three outcomes.

Authors' conclusions
Beta-adrenergic blocker plus 5-isosorbide mononitrate was as effective as endoscopic band ligation for the prevention of oesophageal variceal re-bleeding. Both treatments were associated with few complications.

CRD commentary
The review question was clearly stated and inclusion criteria were appropriately defined. Several relevant sources were searched and no language restrictions were applied. No attempts were made to minimise publication bias and the authors acknowledged the potential for this. Methods were used to minimise reviewer errors and bias in the assessment of validity, but it was not clear whether similar steps were taken for study selection, and such methods were not used for data extraction.

Trial validity was assessed using defined criteria and, although only the aggregate score was presented, scores suggested high-quality trials. Appropriate methods were used for the meta-analyses; heterogeneity was assessed and potential sources of heterogeneity were examined.

The evidence appeared to support the authors’ conclusions, but limitations in review methods and analyses based on findings of no significant difference from a few trials weaken the strength of this evidence.

Implications of the review for practice and research
Practice: The authors stated that beta-adrenergic blocker plus 5-isosorbide mononitrate and endoscopic band ligation can be considered for first-line treatment to prevent oesophageal variceal re-bleeding.

Research: The authors stated that the review findings should be confirmed by further large, multicentre RCTs.

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