Meta-analysis: isosorbide-mononitrate alone or with either beta-blockers or endoscopic therapy for the management of oesophageal varices

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CRD summary
This review reported that isosorbide mononitrate alone or in combination with beta blockers did not appear to reduce bleeding in primary or secondary prevention of oesophageal varices. Survival may have increased in comparison with endoscopic therapy. Further research was required. These cautious conclusions and recommendations for research appear appropriate given the limitations of the evidence.

Authors' objectives
To determine the effects of isosorbide mononitrate alone or in combination with either beta-blockers or endoscopic therapy for the management of patients with oesophageal varices and no previous bleeding (primary prevention) or previous variceal bleeding (secondary prevention).

Searching
Cochrane Hepato-Biliary Group Controlled Trials Register, The Cochrane Library, MEDLINE, EMBASE and Science Citation Index were searched up to January 2010. Search terms were reported. Reference lists of relevant papers, conference abstracts and online trial registers were screened for further studies. Topic experts were contacted. No apparent language or publication restrictions were applied.

Study selection
Randomised controlled trials (RCTs) that assessed the effects of isosorbide mononitrate for patients with oesophageal varices and either no previous bleeding (primary prevention) or previous variceal bleeding (secondary prevention) were eligible for inclusion in the review. Eligible treatment comparisons were isosorbide mononitrate alone or with beta-blockers versus placebo, no intervention, beta-blockers, endoscopic therapy (banding ligation or sclerotherapy), transjugular intrahepatic portosystemic shunts (TIPS) or a combination of isosorbide mononitrate plus beta-blockers and endoscopic therapy. Studies had to report mortality (primary outcome). Secondary outcomes included upper gastrointestinal bleeding, variceal bleeding, bleeding-related mortality and adverse events.

Most of the included studies assessed secondary prevention and others assessed primary prevention. Some primary prevention trials compared isosorbide mononitrate against placebo, beta-blockers or banding ligation; others compared isosorbide mononitrate plus beta-blockers against beta-blockers or banding ligation. Secondary prevention trials compared isosorbide mononitrate plus beta-blockers alone or with banding ligation versus beta-blockers, endoscopic therapy or TIPS. Initial doses of isosorbide mononitrate ranged from 20 to 40mg/day to a maximum of 40 to 80mg/day. Mean dose ranged from 30 to 73mg/day. Beta-blockers assessed included nadolol and propranolol. Initial doses ranged from 40 to 80mg/day. In most trials, dose was adjusted to achieve a resting heart rate of about 55 to 60 beats per minute, 20% to 25% reduction in resting heart rate or a maximum of 160 to 240mg/day if tolerated. Mean dose of beta-blockers ranged from 40 to 125mg/day.

Reported exclusion criteria for participants included contraindications to isosorbide mononitrate or beta-blockers (heart disease with aortic stenosis or atrioventricular block, peripheral ischaemic disease or chronic pulmonary disease), chronic renal failure and malignant disease. In trials on isosorbide mononitrate and beta-blockers, isosorbide mononitrate was initiated after the maintenance dose of beta-blocker was achieved. Patients with cirrhosis comprised 85% to 100% of patients. The proportion of patients with large varices ranged from 36% to 100% in trials on primary prevention and from 77% to 100% in trials on secondary prevention. The mean age of included patients ranged from 51 to 66 years. The proportion of men ranged from 53% to 85%. Trials were performed in Argentina, China, Egypt, France, UK, India, Italy, Pakistan, Spain and Taiwan. Maximum duration of follow-up ranged from eight to 91 months (median 24 months).

Two reviewers assessed the studies for inclusion.
Assessment of study quality
Methodological quality of studies was assessed using criteria for allocation concealment, randomisation methods, blinding, missing outcome data, adequate reporting of outcome measures and adequate sample size.

The authors did not state how many reviewers assessed study validity.

Data extraction
Two reviewers extracted the study data. Authors were contacted for missing information. Missing outcome data were estimated using the last observation carried forward method. Intention-to-treat (ITT) data were used to calculate risk ratios (RRs) with 95% confidence intervals (CIs).

Methods of synthesis
Studies were grouped according to outcome. Risk ratios and 95% CIs were pooled using a random-effects model. Statistical heterogeneity was assessed using the I^2 statistic. Meta-analyses were stratified for all outcome measures except adverse events. Subgroup analyses were conducted for trials of primary and secondary prevention and studies with adequate randomisation. Publication bias was assessed using funnel plots and meta-regression. Post hoc analyses were used to investigate discrepancies between the number of patients and events in abstracts and full papers. Trial sequential analysis was used to account for multiple comparisons for statistically significant outcome measures with alpha set to 5% and power to 80%.

Results of the review
Twenty-seven RCTs (number of participants unclear) were included in the review. Randomisation methods (allocation sequence generation and allocation concealment) were adequate in 17 trials. Adequate double-blinding was used in six trials. Eighteen trials reported sample size calculations. The authors reported that all trials showed evidence of bias.

Primary prevention: 10 RCTs

There were no reported significant differences for any mortality outcome between isosorbide mononitrate and placebo or beta blockers and between isosorbide mononitrate plus beta blockers versus beta blockers. There was no evidence of significant heterogeneity for any analyses (I^2 = 0% to 6%). In single trials, isosorbide mononitrate increased the risk of bleeding compared with placebo (RR 2.34, 95% CI 1.10 to 4.97) and banding ligation (RR 4.33, 95% CI 1.57 to 11.92). There were no significant differences in bleeding between isosorbide mononitrate alone or with beta-blockers or banding ligation. A significant difference was reported for variceal bleeding and this favoured banding ligation in comparison with isosorbide mononitrate (RR 3.31, 95% CI 1.01 to 10.84). No significant differences were reported for the other treatment comparisons.

Secondary prevention: 17 RCTs

Significant differences in mortality were reported in favour of isosorbide mononitrate plus beta blockers versus endoscopic therapy (RR 0.73, 95% CI 0.59 to 0.89). No significant differences were reported for mortality for isosorbide mononitrate versus any other comparator. Risk of bleeding was significant higher for isosorbide mononitrate plus beta blockers versus TIPS (RR 2.94, 95% CI 1.46 to 5.90). Risk of variceal bleeding was increased for isosorbide mononitrate plus beta blockers compared with banding ligation (RR 1.61, 95% CI 1.14 to 2.27) and TIPS (RR 3.03, 95% CI 1.31 to 6.98). No other significant differences were reported for bleeding (variceal bleeding included). Where reported, there was little if any evidence of statistical heterogeneity reported for the analyses.

Additional data were reported for the risk of adverse events and sensitivity analyses. There was little evidence of publication bias.

Authors’ conclusions
Isosorbide mononitrate alone or in combination with beta blockers did not appear to reduce bleeding in primary or secondary prevention of oesophageal varices. Survival may have increased in comparison with endoscopic therapy. Further research was required.
CRD commentary
This review addressed a clearly defined research question and made attempts to locate evidence regardless of language and publication status. Risk of language and publication biases was low. Risk of reviewer error and bias appears to be generally low, although it was unclear whether the reviewers took appropriate precautions when assessing the methodological quality of the included studies. Relevant criteria were used to assess study quality and most studies showed some risk of bias; therefore, the data may not be reliable. There was little evidence of statistical heterogeneity and subgroup analyses. Regression analyses were used to assess some aspects of clinical heterogeneity. Some of the review findings were based on single trials with relatively small sample sizes, which suggested that they may not have been reliable.

The authors cautious conclusions and recommendations for research appear appropriate given the limitations of the evidence.

Implications of the review for practice and research
Practice: The authors stated that there was no evidence to support use of isosorbide mononitrate for prevention of oesophageal varices.

Research: The authors stated that further long-term large multicentre trials of isosorbide-mononitrate were needed for the prevention of oesophageal varices.

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