Variceal band ligation versus beta-blockers for primary prevention of variceal bleeding: a meta-analysis

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CRD summary
The authors concluded that variceal band ligation reduces the risk of a first variceal bleed and adverse events leading to treatment discontinuation compared with beta-blockers in patients with oesophageal varices. Despite limitations in the search and reporting of review methods, overall, the authors’ conclusions appear reliable.

Authors’ objectives
To compare variceal band ligation (VBL) with beta-blockers (BBs) for the prevention of bleeding from oesophageal varices.

Searching
PubMed, MEDLINE, Web of Knowledge and the Cochrane CENTRAL Register were searched from 1995 to 2006 for fully published peer-reviewed studies; the search terms were reported.

Study selection
Study designs of evaluations included in the review
Randomised controlled trials (RCTs) were eligible for inclusion in the review. The duration of follow-up ranged from 13 to 35 months in the included studies.

Specific interventions included in the review
Studies of primary prevention that compared VBL with non-selective BB were eligible for inclusion. The included studies evaluated single- and multi-banded ligators and combinations of these. Ligation was repeated between 1 and 5 weeks. A minority of studies used routine proton-pump inhibitors after VBL. All but one of the included studies compared VBL with propranolol (mean daily dose 60 to 113.5 mg); one study evaluated nadolol. Compliance, which was assessed in all studies, ranged from 91 to 100%.

Participants included in the review
Studies of patients with oesophageal varices, secondary to portal hypertension, who had no evidence of previous variceal bleeding, were eligible for inclusion. The patients in the included studies tended to have moderate to large oesophageal varices. In all but 2 studies, the mean age was above 50 years.

Outcomes assessed in the review
Inclusion criteria were not specified for the outcomes. The review assessed first variceal bleed, overall mortality, bleeding-related mortality and severe treatment-associated adverse events that resulted in treatment withdrawal.

How were decisions on the relevance of primary studies made?
Two reviewers selected the studies. It is unclear whether this was done independently, or how any disagreements were resolved.

Assessment of study quality
Two reviewers assessed studies for adequacy of generation of randomisation, allocation concealment, blinded outcome assessment, intention-to-treat analysis and completeness of follow-up (ideally greater than 90% with no significant difference between treatment groups). The review also assessed the reporting of sample size calculations.

Data extraction
The authors did not state how the data were extracted for the review, or how many reviewers performed the data extraction. Outcome data were extracted as relative risks (RRs).
Methods of synthesis
How were the studies combined?
Pooled RRs and 95% confidence intervals (CIs) were calculated using the random-effects model of DerSimonian and Laird. Where a statistically significant difference between treatments was found, the number-needed-to-treat (NNT) and corresponding 95% CI were calculated. Publication bias was assessed using a funnel plot and the rank correlation test.

How were differences between studies investigated?
Statistical heterogeneity was assessed using the Cochrane chi-squared statistic. Meta-analyses were repeated using a fixed-effect Mantel-Haenszel model and after including all studies published as abstracts. Differences between the studies were discussed in the text.

Results of the review
Nine RCTs (n=734) were included.

Eight studies met at least three of the five quality criteria. Four studies met four quality criteria. Three studies reported drop-outs; all patients were included in the final intention-to-treat analysis. None of the studies reported blinded outcome assessment. Five studies performed sample size calculations.

There was no evidence of heterogeneity or publication bias for any of the analyses. All 9 RCTs contributed to all of the meta-analyses described below.

Patients undergoing VBL were at significantly lower risk of a first variceal bleed than patients receiving BBs (RR 0.63, 95% CI: 0.43, 0.92, p=0.02); the NNT to prevent one first variceal bleed was 13 (95% CI: 7, 33).

There was no statistically significant difference between VBL and BB in overall mortality (RR 1.09, 95% CI: 0.86, 1.38, p=0.47) or bleeding-related deaths (RR 0.71, 95% CI: 0.38, 1.32, p=0.28).

Adverse events that caused treatment discontinuation were reported in 7 patients in the VBL group (5 were due to bleeding from banded ulcers; 2 died) and 53 patients in the BB group (12 who discontinued experienced variceal bleeding). The main adverse events with BB were fatigue, shortness of breath, symptomatic hypotension, bradycardia, first-degree heart block and circulation problems. Patients undergoing VBL were at significantly lower risk of an adverse event leading to treatment discontinuation than patients receiving BB (RR 0.24, 95% CI: 0.12, 0.47, p<0.001); the NNT to prevent one adverse event leading to treatment discontinuation was 10 (95% CI: 6, 25).

Authors’ conclusions
Compared with BBs, VBL reduced the risk of a first variceal bleed and adverse events leading to treatment discontinuation in patients with oesophageal varices.

CRD commentary
The review question was clear with respect to the participants, intervention, outcomes and study design. Limiting the search to fully published peer-reviewed studies raises the possibility of publication bias and might have resulted in the omission of other relevant studies. Publication bias was assessed and no evidence of it was found. It was unclear whether any language restrictions had been placed on the search. Two reviewers selected studies and assessed validity, although it was unclear whether they did this independently, and the methods used to extract the data were not reported. Given this information, one cannot be sure whether efforts were made to reduce reviewer error and bias in the review process. Statistical heterogeneity was assessed and no evidence of it was found, thus it was appropriate to pool the studies using meta-analysis. Differences between the studies were discussed. There were limitations in the search and reporting of review methods but, overall, the authors’ conclusions appear reliable.

Implications of the review for practice and research
Practice: The authors stated that VBL should be offered to patients with moderate to large oesophageal varices who are unlikely to comply with drug treatment; are intolerant of or with contraindications to BB; or who bleed whilst taking
BB. Treatment with BB still has a place for other groups of patients. Account should be taken of patients’ wishes where possible.

Research: The authors did not state any implications for further research.

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