Endoscopic treatment versus endoscopic plus pharmacologic treatment for acute variceal bleeding: a meta-analysis

Authors' objectives
To assess whether vasoactive drugs improve the efficacy of endoscopic therapy (injection sclerosis or band ligation), in terms of the control of acute variceal bleeding and increased overall survival.

Searching
MEDLINE and EMBASE were searched from January 1994 to May 2001 using the terms 'acute variceal bleeding' and 'randomized controlled trial'. The authors also searched the Cochrane Controlled Trials Register, and reviewed abstracts from the meetings of the American Gastroenterological Association, the American Association for the Study of Liver Diseases, the European Association for Study of the Liver, and the British Society of Gastroenterology. The bibliographies from each full-published report were searched manually.

Study selection
Study designs of evaluations included in the review
Randomised controlled trials (RCTs) were included.

Specific interventions included in the review
Combined treatment including endoscopic and drug therapy (octreotide and/or somatostatin, or vapreotide) compared with endoscopic treatment alone. The drug dosages were presented in the paper.

Participants included in the review
Participants with acute variceal bleeding. In the included studies, the patients had oesophageal variceal bleeding or upper gastrointestinal bleeding. Where reported, the mean age of the patients was 52 years, and 61% were men. The proportion of patients with alcoholic cirrhosis was 66% (range: 6 to 86).

Outcomes assessed in the review
The study inclusion criteria required one or more of the following outcome measures:

initial haemostasis, defined as the clinical absence of continued bleeding within 6 to 48 hours of treatment;

haemostasis at day five, defined as the clinical absence of continued bleeding within five days of beginning treatment;

mortality at day five, defined as any death occurring within five days of beginning treatment; and

adverse events.

How were decisions on the relevance of primary studies made?
The authors do not explicitly state how decisions on the relevance of the primary studies were made, although more than one reviewer was involved in the process.

Assessment of study quality
The quality of each trial was assessed using the following criteria: generation of allocation sequence; allocation concealment; investigator blindness; description of withdrawals and drop-outs; and efficacy of randomisation. The scoring system was described within a table. Two reviewers independently assessed the quality of the studies. Any disagreement was resolved by consensus.
Data extraction
Three reviewers independently abstracted quantitative data regarding the number of patients in the treatment groups and the number associated with each outcome. In cases of disagreement, the opinions of all the research team members were sought.

The data tabulated were: study identification; type of publication, i.e. peer-reviewed article or abstract; study design; study population; exclusion criteria; endoscopic therapy; drug therapy; the number of patients; mean age; the percentage of patients with alcoholic cirrhosis; the percentage of patients with Child class C; outcomes; and quality scores.

Methods of synthesis

How were the studies combined?
The pooled relative risk (RR) and 95% confidence intervals (CIs) were calculated using the fixed-effect model and, when statistically heterogeneous, the random-effects model of DerSimonian and Laird (see Other Publications of Related Interest nos.1-2). Where the RR demonstrated a benefit of one treatment, the number-needed-to-treat (NNT) was calculated. Publication bias was assessed according to the file-drawer method (fail-safe N) of Rosenthal (see Other Publications of Related Interest no.3).

How were differences between studies investigated?
Statistical heterogeneity was evaluated using the Cochran chi-squared test (P<0.10 level). The authors also discussed potential sources of clinical heterogeneity between the studies. Sensitivity and subgroup analyses were performed for:

- the type of publication, i.e. excluding manuscripts published as abstracts;
- the drug used, i.e. the exclusion of drugs other than octreotide;
- the dose of octreotide (greater than and lower than 50 microg/hour);
- the proportion of alcoholic patients, i.e. the exclusion of trials with less than 40% alcoholics; and
- the proportion of high-risk cirrhotic patients, i.e. the exclusion of trials with less than 35% Child class C patients.

Results of the review
Eight RCTs with 939 patients were included in the analysis. Five were published in full in peer-reviewed journals and three in abstract form.

The quality scores of the 5 fully-published trials ranged from 5 to 8, out of a possible score of 10. The agreement between the investigators was 100% for the qualitative assessment.

Initial haemostasis (4 RCTs, n=559): initial control of bleeding was achieved in 88% of the patients treated with endoscopy and drugs, and in 76% of those treated with endoscopy alone. The RR of achieving initial control of bleeding with combined therapy was 1.12 (95% CI: 1.02. 1.23) when using the random-effects model, and the NNT was 8 (95% CI: 5, 16). The test for heterogeneity was statistically significant (P=0.94).

Five-day haemostasis (8 RCTs, n=939).

There was no statistically-significant heterogeneity in the results of this variable. In all trials, the control of bleeding at 5 days was achieved in a greater proportion of patients receiving endoscopic plus drug therapy (77%) than those treated with endoscopy alone (58%). The RR was 1.28 (95% CI: 1.18, 1.39) when using the fixed-effect model, and the NNT was 5 (95% CI: 4, 8). Publication bias assessment showed that 152 null or negative studies would be needed to render the result of this analysis non significant.

The difference in favour of combined treatment remained significant when trials that used drugs other than octreotide, or that included a low proportion of alcoholic patients (less than 40%) or of high-risk cirrhotic patients (less than 35%), were excluded from the meta-analyses.
Mortality at 5 days (6 RCTs).

The results from 6 trials demonstrated that mortality was not significantly decreased by combining endoscopic and drug therapy (test for homogeneity, P=0.96; RR 0.73, 95% CI: 0.45, 1.18).

Adverse events.

The results from 3 trials demonstrated that severe adverse events were similar in the drug and control groups. Hyperglycaemia was the most commonly reported mild adverse effect and was shown by 13% of those patients treated with drugs, compared with 8% of those receiving a placebo (test for homogeneity, P=0.51; RR 1.72, 95% CI: 1.00, 2.94).

Authors’ conclusions
In patients with acute variceal bleeding, pharmacological agents improved the efficacy of endoscopic therapy to achieve initial control of bleeding and 5-day haemostasis, yet they failed to affect mortality.

CRD commentary
The review question and the inclusion criteria were clearly stated in terms of the study design, participants, intervention and outcomes of interest. The authors searched for relevant literature using two databases, by reviewing conference abstracts, and by handsearching bibliographies. However, they do not state whether any language restrictions were applied, and they do not justify why the search dates were relatively narrow. The validity of the included studies was adequately assessed, with more than one reviewer performing the quality assessment. Sufficient details of the individual studies were presented, and the studies were summarised appropriately.

The conclusions of the review follow from the results.

Implications of the review for practice and research
Practice: The authors did not state any implications for practice.

Research: The authors state that more trials are needed to unequivocally determine further potential advantages of combined therapy.

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Other publications of related interest
This additional published commentary may also be of interest. Srivastava A. Endoscopic treatment versus endoscopic plus pharmacologic treatment for acute variceal bleeding: a meta-analysis. Indian J Gastroenterol 2002;21:169.

**Indexing Status**
Subject indexing assigned by NLM

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