An evaluation of emergency sclerotherapy of varices in randomized trials: looking the needle in the eye

CRD summary
This review assessed the role of sclerotherapy, compared with vasoactive drugs and ligation, for acute variceal bleeding. The authors concluded that, while emergency treatment with sclerotherapy at the time of the initial endoscopy should remain as first-line treatment, further research of ligation and vasoactive drugs is required. Despite some methodological limitations, the authors' conclusion seems appropriate.

Authors' objectives
To determine whether emergency sclerotherapy remains the 'gold' standard for the treatment of bleeding oesophageal varices, for both the control of acute bleeding and prevention of early bleeding.

Searching
MEDLINE and EMBASE were searched from January 1980 to May 2005; the search terms were reported. The references of all relevant articles were also checked. Conference proceedings (1995 to May 2005) of the American Association for the Study of Liver Diseases and the European Association for the Study of the Liver, and from Digestive Diseases Weeks and United Gastroenterology Weeks, were also searched.

Study selection
Randomised controlled trials (RCTs) were eligible for inclusion in the review; studies in which randomisation occurred on the third day or 24 hours after bleeding stopped were excluded. Studies that compared sclerotherapy with vasoactive agents or variceal ligation were also eligible for inclusion. Studies in which sclerotherapy was performed only when treatment failure had occurred, or when they was no information on the type of endoscopic therapy, were excluded from the review. The included studies compared sclerotherapy combined with vasoactive agents and/or balloon tamponade with vasoactive agents and/or balloon tamponade alone; sclerotherapy with vasoactive agents; sclerotherapy with sclerotherapy combined with vasoactive agents; and sclerotherapy with variceal ligation. Studies of participants with acute oesophageal variceal bleeding were eligible for inclusion. Studies with fewer than 2% noncirrhotic patients were considered to have a solely cirrhotic population. Studies reporting clinical end points of death and failure to control bleeding (either during drug infusion, or initial haemostasis when sclerotherapy is compared with ligation) and/or the prevention of early re-bleeding (within 5 to 7 days) were eligible for inclusion. Bleeding end points were not the same in each study but were always defined using accepted clinical criteria.

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

Assessment of study quality
The quality of the primary studies appears to have been evaluated according to Papatheodoridis et al. (1999). The authors did not report the criteria by which these studies were assessed. A summary score was calculated for each study; highest and lowest possible scores were not specified. Only median scores and range of summary score for each meta-analytic group category were presented.

Three reviewers independently assessed the quality of the included studies.

Data extraction
Three reviewers independently extracted the data from the included studies, and any disagreements were resolved by discussion.

Methods of synthesis
The studies were combined in a meta-analysis grouped by treatment/comparator and outcome. Summary estimates were reported as the risk difference (absolute risk reduction, RD) with 95% confidence intervals (CIs). Where there was statistical significance the number-needed-to-treat (NNT) was calculated. Statistical heterogeneity was assessed using the Q test. Sensitivity analyses for failure to control bleeding and for death were performed in terms of type of publication (full paper or abstract), type of vasoactive agent, duration of drug infusion and aetiology of liver disease (i.e. cirrhosis alone or cirrhotic/noncirrhotic liver disease). Publication bias appears to have been assessed.

**Results of the review**

Forty studies (n=4,031) were included in the review.

The quality score for the included trials ranged from 49 to 79. The authors reported that the time interval for evaluating transfusion requirement varied across studies, both before and after randomisation, and means and medians were not consistently used; transfusion requirements could therefore not be evaluated statistically.

Sclerotherapy combined with vasoactive agents and/or balloon tamponade versus vasoactive agents and/or balloon tamponade alone.

Failure to control bleeding (5 studies, 413 episodes): there were 214 episodes of variceal bleeding in the sclerotherapy group and 199 episodes in the control group. Failure to control bleeding was significantly less frequent in the sclerotherapy group (RD 16.3%, 95% CI: 8.7, 23.9); the NNT was 6 (95% CI: 4, 11). Evidence of statistical heterogeneity was not reported. Sensitivity analyses did not alter the results.

Mortality (5 studies, n=413): there was no statistically significant difference between treatment groups (RD 5.5%, 95% CI: -1.8, 12.7); there was no evidence of significant statistical heterogeneity. Sensitivity analyses did not alter the results.

Complications (3 studies): insufficient data were reported.

Sclerotherapy versus vasoactive agents.

Failure to control bleeding (15 studies, 1,322 episodes): there were 668 episodes of variceal bleeding in the sclerotherapy group and 654 episodes in the control group. Failure to control bleeding was less frequent in the sclerotherapy group (RD 5.9%, 95% CI: 1.5, 10.3); there was evidence of significant statistical heterogeneity. When the analysis was repeated with the exclusion of data from abstracts, no statistically significant between-group difference was found (RD 3.4%, 95% CI: -1.8, 8.5).

Mortality (15 studies, n=1,322): fewer deaths with sclerotherapy were found (RD 4.3%, 95% CI: 0.6, 8.1); there was no evidence of significant statistical heterogeneity. The NNT was 23 (95% CI: 12, 157). Sensitivity analyses did not significantly alter the results.

Complications (12 studies): these were less frequent with any vasoactive drug (RD 8.8%, 95% CI: 0.2, 15.6); there was evidence of significant statistical heterogeneity.

Sclerotherapy versus sclerotherapy combined with vasoactive agents.

Failure to control bleeding (8 studies, 1,056 episodes): there were 525 episodes of variceal bleeding in the sclerotherapy group and 531 in the control group. Failure to control bleeding was less frequent in the sclerotherapy group (RD 13.2%, 95% CI: 8.4, 18.1). The NNT was 8 (95% CI: 5, 15). Sensitivity analyses did not alter the results.

Mortality (7 studies, n=968): no statistically significant difference between treatment groups was found (3.4%, 95% CI: -0.4, 7.1).

Complications (5 studies): only 2 studies reported data per patient; no statistically significant between-group differences were reported.

Sclerotherapy versus variceal ligation.
Failure to control bleeding (12 studies, 1,303 episodes): there were 652 episodes of variceal bleeding in the sclerotherapy group and 651 in the control group. Failure to control bleeding was less frequent in the ligation group (RD 2.5%, 95% CI: 0.4, 4.6). Sensitivity analyses did not alter the results.

Mortality (7 studies, n=817): the difference was 1.3% (95% CI: -2.3, 4.9) in favour of ligation, although this was not statistically significant. Sensitivity analyses did not alter the results.

Authors' conclusions

Emergency treatment with sclerotherapy, at the time of the initial endoscopy when the source of bleeding is to be diagnosed, should remain as first-line treatment. However, further studies of ligation and vasoactive drugs are required.

CRD commentary

The review question was supported by clear inclusion and exclusion criteria. Several sources were searched for relevant articles; it is unclear if the search was restricted by language. The authors stated that they assessed publication bias, although it is not clear how they did this. Methods undertaken to extract the data and assess study validity were likely to have minimised error and bias. It is not clear whether similar methods were used to select papers for inclusion in the review. The authors did not report what criteria were used to assess the validity of the included studies. In addition, it is not clear what the reported median and range of summary scores represent, as highest and lowest possible values were not given. Few details were given of the study characteristics and populations. The studies were combined using standard meta-analytic methods, although it appears as if participants from one study were double counted in one of the meta-analytic groups. Statistical heterogeneity was assessed, but not always reported, and the authors investigated potential sources of heterogeneity. Whilst there were a number of methodological limitations that restrict interpretation of the results, there is no evidence to support a change in practice and a need for further research and the authors’ conclusions reflect this.

Implications of the review for practice and research

Practice: The authors stated that emergency treatment with sclerotherapy, at the time of the initial endoscopy when the source of bleeding is to be diagnosed, should remain as first-line treatment.

Research: The authors stated that the use of an additional pharmacologic agent given as soon as possible after admission, before diagnostic endoscopy, should be be investigated in further RCTs. In addition, the authors stated the need for greater standardisation of definitions and a consensus for the reporting of blood transfusion requirements.

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