Octreotide for acute esophageal variceal bleeding: a meta-analysis

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Authors' objectives
To evaluate the safety and efficacy of octreotide for esophageal variceal haemorrhage.

Searching
The following databases were searched from 1985 to 1999: MEDLINE (using 'clinical trial' combined with 'octreotide' or 'somatostatin'); the Cochrane Library (keyword 'octreotide'); and EMBASE (subject heading 'gastrointestinal haemorrhage' and keyword 'octreotide' combined with clinical trial categories). The abstracts and bibliographies of identified studies were manually searched. Experts and Novartis (the manufacturer of octreotide) were contacted for unpublished data. Studies reported in any language were considered.

Study selection
Study designs of evaluations included in the review
Randomised controlled trials (RCTs) with at least 48 hours' follow-up were eligible. The duration of follow-up, where stated, ranged from 5 to 60 days.

Specific interventions included in the review
Studies that examined the use of octreotide for acute variceal haemorrhage were eligible. Octreotide for the prevention of re-bleeding or non-variceal upper gastrointestinal haemorrhage was excluded. Octreotide was given in the following regimens: intravenous bolus of 50 to 100 microg followed by 25 to 50 microg/hour intravenously; continuous intravenous infusion (25 to 50 microg/hour); and 100 microg subcutaneously every 8 hours (one study). The mean dose per hour ranged from 13 to 51 microg. The duration of therapy ranged from 8 to 168 hours.

The alternative therapies were vasopressin, terlipressin with or without transdermal nitroglycerine, balloon tamponade, sclerotherapy, placebo and no treatment. The cointerventions included initial sclerotherapy or banding and sclerotherapy to all study participants after 48 hours.

Participants included in the review
Patients with acute variceal haemorrhage were eligible if endoscopy confirmed esophageal varices as the probable bleeding source. Trials including non-variceal upper gastrointestinal haemorrhage were excluded. The percentage of patients categorised as Child's C ranged, where reported, from 10 to 62.5% in the octreotide group, and from 13 to 75% in the alternative treatment groups.

Outcomes assessed in the review
Studies that provided raw data on overall mortality and/or the control of bleeding were eligible. The following primary outcomes were assessed: overall mortality (from any cause); sustained control of bleeding (absence of re-bleeding as defined in each study); any complication (excluding post-sclerotherapy ulcerations); and major complications.

How were decisions on the relevance of primary studies made?
All identified article titles and available abstracts were reviewed. The authors do not state how many of the reviewers performed the selection.

Assessment of study quality
Validity was assessed using the adequacy of randomisation and blinded allocation to treatment groups. The adequacy of randomisation was assessed using each author's assessment of the statistical equivalence of baseline factors in the treatment groups. Two authors, who were blinded to the journal, year of publication and authors, independently abstracted the quality data. Any disagreements were resolved by consensus with a third reviewer.
**Data extraction**
Two authors, who were blinded to the journal, year of publication and authors, independently abstracted the outcome data. Any disagreements were resolved by consensus with a third reviewer.

The following information were tabulated in the review: the author; characteristics of the octreotide intervention (dose, duration, and route); total follow-up period; alternative intervention; the number of patients per intervention group; and the percentage Child C in each intervention group. Where multiple publications were identified, data from the most recent publications were used. For trials with multiple interventions, comparisons of octreotide with placebo were used.

**Methods of synthesis**
How were the studies combined?
Pooled relative risks (RRs) and 95% confidence intervals (CIs) were calculated using the fixed-effect Mantel-Haenszel method. Intention-to-treat analyses were performed for all studies together and by considering three major alternative interventions. These were vasoactive agents (vasopressin or terlipressin); immediate and follow-up sclerotherapy (octreotide patients received sclerotherapy only after the study period infusion of octreotide); and placebo or no intention (all patients received initial sclerotherapy or banding and were then randomised to octreotide or placebo/no intervention).

Publication bias was assessed by two methods. Firstly, by calculating the correlation coefficient between the risk ratio and sample size. Secondly, by calculating the number of unpublished negative studies (NNS) required to nullify any significant results. There was no evidence for publication bias either for the primary outcome of sustained control of bleeding (p = 0.16 to 0.31) or after calculating the NNS.

How were differences between studies investigated?
Statistical heterogeneity was assessed for all summary RR estimates; a p-value of less than or equal to 0.1 was considered significant. The results from fixed-effect and random-effects models were compared. The studies were stratified by liver disease severity and summary estimates were calculated. Sensitivity analyses were conducted by excluding studies without blinded allocation and adequate randomisation, and by comparing studies with and without explicitly defined re-bleeding criteria.

**Results of the review**
Thirteen RCTs (1,077 patients) were included.

Overall mortality.

There was no significant difference between octreotide compared with any alternative intervention, for octreotide compared with vasopressin or terlipressin, or for octreotide compared with placebo or no intention. Octreotide versus any alternative therapy (11 RCTs, 948 patients).

The RR was 0.89 (95% CI: 0.69, 1.14). The homogeneity p was 0.3.

Octreotide versus vasopressin or terlipressin (4 RCTs, 236 patients).

The RR was 0.80 (95% CI: 0.54, 1.19). The homogeneity p was 0.88.

Octreotide versus placebo or no therapy after all received initial sclerotherapy or banding (4 RCTs, 424 patients).

The RR was 0.81 (95% CI: 0.48, 1.35). The homogeneity p was 0.6.

Octreotide versus sclerotherapy (2 RCTs, 248 patients).

The RR was 1.1 (95% CI: 0.73, 1.66). There was evidence of heterogeneity (p=0.02), hence specific statements could not be made.
Sustained control of bleeding.

Octreotide was associated with a significant reduction in the risks of re-bleeding compared with any alternative intervention, for octreotide compared with vasopressin or terlipressin, and for octreotide compared with placebo or no treatment. There was no significant difference between octreotide and sclerotherapy. There was no evidence of heterogeneity for any of these comparisons.

Octreotide versus any alternative therapy (13 RCTs, 1,077 patients).

The RR was 0.63 (95% CI: 0.51, 0.77). The homogeneity p was 0.2.

Octreotide versus vasopressin or terlipressin (5 RCTs, 279 patients).

The RR was 0.58 (95% CI: 0.42, 0.81). The homogeneity p was 0.97.

Octreotide versus placebo or no therapy after all received initial sclerotherapy or banding (5 RCTs, 510 patients).

The RR was 0.46 (95% CI: 0.32, 0.67). The homogeneity p was 0.4.

Octreotide versus sclerotherapy (2 RCTs, 248 patients).

The RR was 0.94 (95% CI: 0.55, 1.62). The homogeneity p was 0.6.

Any complications.

Any complications were more common among those receiving vasopressin or terlipressin than octreotide. There was no significant difference between octreotide compared with any alternate therapy, for octreotide compared with placebo or no therapy, or for octreotide compared with sclerotherapy. There was evidence of significant heterogeneity among studies for octreotide versus any alternative therapy and for octreotide versus sclerotherapy, hence specific conclusions about these comparisons could not be made. Octreotide versus any alternative therapy (11 RCTs, 948 patients).

The RR was 0.77 (95% CI: 0.6, 1.00). The homogeneity p was less than 0.001. Octreotide versus vasopressin or terlipressin (4 RCTs, 236 patients).

The RR was 0.52 (95% CI: 0.33, 0.82). The homogeneity p was 0.13.

Octreotide versus placebo or no therapy after all received initial sclerotherapy or banding (4 RCTs, 424 patients).

The RR was 1.06 (95% CI: 0.72, 1.55). The homogeneity p was 1.

Octreotide versus sclerotherapy (2 RCTs, 248 patients).

The RR was 0.91 (95% CI: 0.5, 1.65). The homogeneity p was less than 0.001.

Major complications.

Major complications were more common for vasopressin or terlipressin than with octreotide, but not for any of the other comparisons.

Octreotide versus vasopressin or terlipressin (4 RCTs, 236 patients).

The RR was 0.31 (95% CI: 0.11, 0.87). The homogeneity p was 0.6.

All significant results found when using fixed-effect models were also significant when using random-effects models.

Sensitivity analyses.
Restricting the analyses to studies with adequate investigator blinding and adequate randomisation resulted in a barely significant reduction in mortality for octreotide versus any alternative therapy (previously, mortality was not significantly different between the groups), but it did not change the magnitude or significance of other summary results.

Octreotide versus any alternative therapy.

The RR was 0.76 (95% CI: 0.58, 1.0). The homogeneity p was 0.86.

After excluding 2 studies with a low proportion of patients with severe liver disease (less than 40% with Child C disease), there was no change in the magnitude or significance of summary estimates for sustained control of bleeding, major complications, or total mortality for octreotide versus any alternate therapy or for any other comparison.

The authors reported the following limitations of the review: the variation in alternative therapies, both between and within the subgroups; there were relatively few trials of each alternative intervention; the potential for publication bias; an inability to confirm whether complications were reported on a per-patient basis; the variability in the patient populations; the variability in the quality of the included studies; and inconsistent use of a standard definition of re-bleeding.

Authors' conclusions
The results suggested that octreotide is more effective than vasopressin or terlipressin in the control of oesophageal variceal bleeding, and that it is a safe and effective adjuvant therapy after variceal obliteration techniques.

CRD commentary
The aims were stated and the inclusion criteria were defined in terms of the participants, intervention, outcome and study design. Several relevant sources were searched, attempts were made to locate unpublished material, and no language restrictions were applied. The studies were restricted to RCTs and validity was assessed using specified methods. Relevant information on the primary studies was presented in tabular format and in the text, and the methods used to extract the data were described. The data were pooled in a meta-analysis and statistical heterogeneity was assessed. Sensitivity analyses were used to examine the influence of various factors, including study validity, on the results.

Where evidence of statistical heterogeneity was found, the authors advised caution in the interpretation of the results. The limitations of the review were discussed in the text of the review.

The evidence presented supports the authors' conclusions.

Implications of the review for practice and research
Practice: The authors state that the results suggest that octreotide is favoured over vasopressin or terlipressin for both efficacy and safety in patients with acute oesophageal variceal bleeding. In addition, that octreotide is an effective adjuvant therapy after initial variceal sclerotherapy or band ligation techniques.

Research: The authors state that further trials are required to determine the optimal dose, route and duration of octreotide therapy.

Funding
American Digestive Health Foundation Outcomes Research Training Award; National Institutes of Health Institutional Training Grant; National Institutes of Health Mentored Clinical Scientist Award; Novartis Pharmaceuticals, East Hanover, NJ.

Bibliographic details

PubMedID
11231948

Indexing Status
Subject indexing assigned by NLM

MeSH
Acute Disease; Esophageal and Gastric Varices /complications; Hemorrhage /drug therapy /etiology /mortality; Hemostatics /adverse effects /therapeutic use; Humans; Lypressin /adverse effects /analogs & derivatives /therapeutic use; Octreotide /adverse effects /therapeutic use; Recurrence; Vasopressins /adverse effects /therapeutic use

AccessionNumber
12001000786

Date bibliographic record published
30/11/2002

Date abstract record published
30/11/2002

Record Status
This is a critical abstract of a systematic review that meets the criteria for inclusion on DARE. Each critical abstract contains a brief summary of the review methods, results and conclusions followed by a detailed critical assessment on the reliability of the review and the conclusions drawn.