Meta-analysis: vasoactive medications for the management of acute variceal bleeds
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CRD summary
Compared to control, vasoactive agents were associated with a significant reduction in acute all-cause mortality and transfusion requirements, improved bleeding control and shorter hospital stay. Studies that compared different vasoactive treatments did not demonstrate a difference in efficacy. Despite limited information on the quality of the studies the conclusions of this review are likely to be reliable.

Authors' objectives
To evaluate the efficacy of vasoactive medications in adult patients with acute variceal bleeds.

Searching
Nine electronic databases including MEDLINE and EMBASE were searched up to September 2011 without language restrictions. Search terms were reported. Experts were consulted for incomplete and unpublished literature. Reference lists and related articles of included studies were consulted. Study authors were contacted for further data.

Study selection
Randomised controlled trials (RCTs) that compared intravenous vasoactive agents to placebo or routine medical care alone were eligible for inclusion. Patients were eligible if they were adults with upper gastrointestinal bleeding presumed or confirmed to be variceal. Diagnostic or therapeutic endoscopy was allowed if both intervention and control groups were treated equally. Trials that compared vasoactive medications administered intra-arterially were excluded.

Mean age of participants was between 39 and 61 years. Where reported, the proportion of patients with a Child-Pugh score of C varied widely (23.8% to 100%) and cirrhosis aetiology varied within and between the trials. Some studies reported diagnostic or therapeutic endoscopy co-treatment for all study arms. Various medications were evaluated and these included octreotide, somatostatin (alone or combined with octreotide), vasopressin, terlipressin and vapreotide. Studies compared vasoactive medications with each other or with placebo. Dosing regimens varied. Studies were published between 1977 and 2008.

Two reviewers independently selected the studies for inclusion. Disagreements were resolved by discussion and a third reviewer was consulted as necessary.

Assessment of study quality
Risk of bias within the studies was assessed and covered randomisation methods, allocation concealment, blinding, intention-to-treat, premature ending of trial and funding source. Where possible, the GRADE approach was used to rate the risk of bias for each outcome.

Data extraction
Outcome measures (acute seven-day mortality, intermediate mortality, hospital stay, transfusion requirements, re-bleeding, arrest of bleeding, stroke, venous thromboembolism and myocardial infarction) were extracted to calculate risk ratios (RRs) and mean differences (MDs).

Two reviewers independently extracted study data. Disagreements were resolved via discussion and a third reviewer was consulted as necessary.

Methods of synthesis
Risk ratios and mean differences were pooled using a Mantel-Haenszel random-effects method. All analyses were performed on an intention-to-treat basis. Heterogeneity was assessed using $I^2$ and explored using subgroup analyses. Differences in vasoactive agents, causes of cirrhosis and length of follow-up were prespecified as important potential sources of heterogeneity. Funnel plots were used to assess the risk of publication bias for all outcomes.

Results of the review
Fifty-seven trials were included. Thirty trials compared vasoactive medications with placebo or standard therapy (3,111 patients) and 27 trials (2,293 patients) compared vasoactive medications with each other. Quality of evidence was rated from very low to moderate. Allocation concealment methods were not used in four studies and were not clearly described in 10 trials. The use of intention-to-treat analysis was absent from one trial and was unclear in 13 studies. Funnel plots showed no evidence of publication bias.

**Mortality:** Compared with control, vasoactive agents were associated with a significant reduction in risk of all-cause mortality within seven days (RR 0.74, 95% CI 0.57 to 0.95; I²=0%; 19 studies). A trend that favoured treatment compared to control in terms of risk of intermediate all-cause mortality at eight to 42 days was not statistically significant (RR 0.80, 95% CI 0.64 to 1.00; I²=21%; 20 studies). The overall quality of the evidence was rated as moderate.

**Other outcomes:** Vasoactive agents were associated with a statistically significant increase in haemostasis (RR 1.21, 95% CI 1.13 to 1.30; I²=27%; 25 studies), the overall quality of this evidence was classed as very low. Risk of re-bleeding was statistically significantly lower for patients who received the intervention (RR 0.68; 95% CI 0.52 to 0.90; I²=41%; 16 studies), the overall quality of this evidence was classed as low.

Patients who received vasoactive medications had transfusion requirements that were statistically significantly lower than control (-0.70 units of blood, 95% CI -1.01 to -0.38; I²=82%; 21 studies). The quality of this evidence was classed as moderate.

Length of hospital stay was lower for patients treated with vasoactive agents, and the difference with control was statistically significant (MD -0.71 days; 95% CI -1.23 to -0.19; I²=0%; four studies). The quality of the evidence was rated as low. Results of subgroup analyses were reported.

**Comparisons between vasoactive treatments:** No difference in mortality or re-bleeding was found between vasoactive treatments. Haemostasis was significantly greater in patients treated with octreotide compared with vasopressin (RR 1.31; 95% CI 1.10 to 1.56; two studies) and significantly lower with vasopressin compared to somatostatin (RR 0.75, 95% CI 0.61 to 0.92; six studies).

**Authors’ conclusions**

Compared to control, vasoactive agents were associated with a significant reduction in acute all-cause mortality and transfusion requirements, improved bleeding control and shorter hospital stay. Studies that compared different vasoactive treatments did not demonstrate a difference in efficacy.

**CRD commentary**

The review question and inclusion criteria were clear. Several bibliographic sources were consulted and the literature searches appeared thorough. Appropriate steps were taken to reduce the risk of error and bias during study selection and data extraction. The authors did not state how many reviewers performed the quality assessment and reporting of the validity assessment was limited (not reported for each individual study) so the actual quality of the evidence was unclear. The methods used to pool the studies and explore heterogeneity appeared appropriate. Where reported, there was evidence of low to moderate heterogeneity between the studies except for one that reported high levels of heterogeneity. Although many studies included limited numbers of patients, the number of studies included in the analyses was generally large and all included studies were RCTs.

Although there are some concerns about heterogeneity in one analysis and a lack of clarity about the reporting of the quality assessment results and process, the conclusions of this otherwise well-conducted review are likely to be reliable.

**Implications of the review for practice and research**

**Practice:** The authors stated that data on the risk of adverse vascular events was limited but there was enough evidence to recommend use of vasoactive agents in clinical practice and as reflected in current guidelines.

**Research:** The authors stated a need for a well-conducted RCT of the combination of two vasoactive agents that was sufficiently powered to detect a difference in clinically relevant outcomes to clarify the benefits and risks of the current standards of care in the management of patients with acute variceal bleeding.
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