Systematic review of randomized trials on vasoconstrictor drugs for hepatorenal syndrome
Gluud LL, Christensen K, Christensen E, Krag A

CRD summary
This generally well-conducted review concluded that terlipressin (a vasoconstrictor drug) plus albumin may prolong short-term survival in type 1 hepatorenal syndrome. Duration of response should be considered for treatment decisions and the timing of potential liver transplantation. The authors’ conclusions should be interpreted with caution given the limited evidence available and the poor quality of included trials.

Authors' objectives
To investigate the effect of vasoconstrictor drugs for the treatment of hepatorenal syndrome.

Searching
MEDLINE, EMBASE, the Cochrane Library and the Cochrane Hepato-Biliary Group Controlled Trials Register were searched to June 2009 for published trials and abstracts in any language. Search terms were not reported. Handsearching included scanning reference lists of included trials, conference proceedings, registers of ongoing trials and correspondence with experts.

Study selection
Randomised controlled trials (RCTs) of vasoconstrictor drugs (with or without albumin) compared with no intervention or albumin in patients with type 1 or 2 hepatorenal syndrome were eligible for inclusion. Trials comparing different vasoconstrictor drugs or modes of administration were also eligible for inclusion.

The primary outcome was all-cause mortality. Secondary outcomes included reversal of hepatorenal syndromes (defined as serum creatinine less than 1.5mg/dL/133µmol/L), improvement in renal function (as defined by authors of included trials), serum creatinine, and adverse events.

In most included trials, patients had type 1 hepatorenal syndrome; a few trials reported 31 to 56% of included patients had type 1 hepatorenal syndrome. In the remaining trials, the type of hepatorenal syndrome was classified based on disease progression (type 1 within two weeks; type 2 over more than two weeks). The definition of type 2 hepatorenal syndrome included elevated serum creatinine above 175µmol/L (1.97mg/dL) and the absence of bacterial infection associated with findings of a systemic inflammatory response (in one trial).

The treatment comparisons assessed included: terlipressin (1mg twice or four times daily) alone or plus albumin versus no intervention, albumin or noradrenalin plus albumin; octreotide (50µg/hour) plus albumin versus albumin; and terlipressin plus albumin administered as continuous or bolus infusion. The dose of noradrenalin was adjusted to achieve an increase in the mean arterial pressure by about 10mmHg. Maintenance doses of albumin ranged from 20 to 60g/day. Where reported, treatment duration ranged from two to 19 days.

The authors did not state how the studies were selected for the review.

Assessment of study quality
Methodological quality was assessed using the following criteria; randomisation, allocation concealment, blinding, withdrawals and drop-outs. Randomisation was classified as the primary measure of bias control.

The authors did not report how many reviewers performed the validity assessment.

Data extraction
Three independent reviewers extracted the number of patients experiencing an event to allow calculation of relative risks (RRs) for binary data, and mean differences and standard deviations to calculate weighted mean differences (WMD) for continuous outcomes. Authors of included trials were contacted for additional information where
necessary. Data were extracted on an intention-to-treat basis. For patients with missing data, carry-forward of the last observed response was used. Only data from the first period of crossover trials were included.

Methods of synthesis
The trials were combined using meta-analyses. The pooled relative risks and corresponding 95% confidence intervals were calculated for binary variables. Pooled weighted mean differences and corresponding 95% confidence intervals were calculated for continuous variables. A random-effects model was used due to the expected heterogeneity. Analyses were conducted by intention to treat. Statistical heterogeneity was assessed using the $I^2$ test.

Post-hoc analyses were conducted to evaluate the relationship between the treatment effect on mortality and the duration of follow-up.

Results of the review
Ten RCTs (n=376 patients) were included in the review. Overall trial quality was poor. Three of the ten trials adequately reported randomisation and allocation concealment. Three trials reported double-blinding; one trial reported single blinding. All but one trial included 52 participants or less.

Vasoconstrictor drugs alone or with albumin significantly reduced mortality (RR 0.82, 95% CI 0.70 to 0.96; six trials), increased the proportion of patients with reversal of hepatorenal syndromes (RR 3.76, 95% CI 2.21 to 6.39; four trials), or improved renal function (RR 2.00, 95% CI 1.11 to 3.62; four trials), compared with no intervention or albumin. No significant heterogeneity was detected.

Subgroup analysis found a beneficial effect of terlipressin alone or with albumin (RR 0.80, 95% CI 0.66 to 0.97). Subgroup analysis of patients with type 1 hepatorenal syndrome showed a beneficial effect for vasoconstrictor drugs plus albumin (RR 0.77, 95% CI 0.61 to 0.98).

Treatment groups had significantly higher risk of cardiovascular events (RR 9.00, 95% CI 2.14 to 37.85), but a no significant increased risk of abdominal pain and diarrhoea (RR 6.82, 95% CI 0.79 to 59.15). No significant heterogeneity was observed. There were no differences between treatment and control groups for any of the remaining adverse events, such as hepatic encephalopathy and bacterial infections.

Post-hoc analysis suggested that the effect on mortality was seen at 15 days (RR 0.60, 95% CI 0.37 to 0.97), but not at 30 days (RR 0.74, 95% CI 0.40 to 1.39), 90 days (RR 0.89, 95% CI 0.66 to 1.22), or 180 days (RR 0.83, 95% CI 0.65 to 1.05).

Authors' conclusions
Terlipressin plus albumin may prolong short-term survival in type 1 hepatorenal syndrome. The duration of the response should be considered when making treatment decisions and in the timing of potential liver transplantation.

CRD commentary
This review addressed a clear question supported by appropriate inclusion criteria. Relevant databases were searched, and attempts were made to minimise publication bias. The authors did not perform a formal assessment of the risk of publication bias due to the small number of included trials. Suitable methods to minimise risk of reviewer error and bias were reported for data extraction, but not for study selection or validity assessment.

Results were pooled using meta-analysis and heterogeneity was assessed. Although vasoconstrictor drugs appeared to be beneficial, the rate of adverse events was high; the authors address this in their discussion where they make recommendations for practice. The authors recognised some of the methodological difficulties with the review, specifically: the poor quality and small number of participants in included trials, the difficulty in diagnosing hepatorenal syndrome, and problems in the recruitment of patients with this condition.

This review was generally well conducted, but the authors' conclusions should be interpreted with caution given the limited evidence available and the poor quality of included trials.
Implications of the review for practice and research

**Practice:** The authors stated that the monitoring of patients should include electrocardiography to detect cardiac ischaemia or arrhythmia, especially in patients with hepatic encephalopathy or diabetes. Likewise, frequent observation to detect peripheral ischaemia with cyanosis, livedo reticularis or skin necrosis of the fingers or extremities is necessary. Patients should be informed of the potential adverse events.

**Research:** The authors stated that future trials may explore potential predictors of a beneficial response, as well as phase IV studies to determine the treatment effect and risk of adverse events in non-specialised units. The combined evidence suggests that additional trials are needed to further optimize the treatment of patients with hepatorenal syndromes.

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