Terlipressin for hepatorenal syndrome: a meta-analysis of randomized trials

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CRD summary
The review concluded that terlipressin had higher efficacy than placebo in reversing renal function in the hepatorenal syndrome population, but that there was no apparent impact on survival. In light of the possibility of relevant studies being missed during the searches and the lack of a trial quality assessment, the authors' conclusions should be interpreted with caution.

Authors' objectives
To evaluate the safety and efficacy of terlipressin in patients with hepatorenal syndrome.

Searching
MEDLINE, EMBASE, Current Contents, and the Cochrane Library were searched for peer-reviewed papers published in English from 1990 to July 2008; search terms were reported. Manual searches of speciality journals were made. Reference lists from reviews and published trials were also searched. Studies published as abstracts or interim reports were not eligible.

Study selection
Prospective clinical trials comparing terlipressin with placebo in patients with hepatorenal syndrome were eligible for inclusion. Trials also had to report response rate.

The primary outcome was risk of hepatorenal syndrome reversal (which was defined as a decrease of serum creatinine to 1.5mg/dL or lower at the end of treatment). Secondary outcomes of interest were side effects and survival.

Most included patients had type-1 hepatorenal syndrome; their mean ages ranged from 50.6 to 60 years. The percentage of male patients ranged from 38 to 75%. Baseline serum creatinine levels (in treatment arms) ranged from 2.2 to 4.1mg/dL. Doses and regimens of terlipressin varied; duration of treatment ranged from two to 15 days. All but one trial allowed concomitant albumin use.

It appeared that two reviewers selected studies for inclusion in the review.

Assessment of study quality
The authors did not formally assess study quality, although level of blinding was stated.

Data extraction
Intention-to-treat data was extracted in order to calculate odd ratios (OR) and 95% confidence intervals (CI).

Two reviewers independently extracted data, with disagreements resolved by consensus.

Methods of synthesis
Pooled odds ratios were calculated using a random-effects model. Heterogeneity was assessed using a Galbraith plot, the Cochran Q test, and the $I^2$ statistic. Sensitivity analyses were performed using a fixed-effect model. Publication bias was assessed using the Klein formula and a funnel plot.

Results of the review
Five randomised controlled trials (RCTs, n=252 patients) were included in the review, with sample sizes ranging from 18 to 112 participants. One RCT had a cross-over design. Two RCTs were double-blinded and two were single-blinded (details not reported for the remaining trial).

The pooled odds ratios for hepatorenal syndrome reversal (OR 8.09, 95% CI 3.521 to 18.59; five RCTs) and survival
(OR 2.064, 95% CI 0.939 to 4.538) indicated benefit after treatment with terlipressin. Both funnel plots indicated the possibility of publication bias. The pooled odds ratio for severe ischaemic events was 2.907 (95% CI 1.094 to 7.723; three RCTs), with no significant publication bias detected. No statistically significant heterogeneity was found for any of the results.

A sensitivity analysis, which excluded the trial not using albumin expansion, resulted in a similar effect size for hepatorenal syndrome reversal (OR 7.3, 95% CI 3.077 to 17.377; four RCTs).

**Authors’ conclusions**
Terlipressin had higher efficacy than placebo in reversing renal function in the hepatorenal syndrome population, but there was no apparent impact on survival.

**CRD commentary**
The review addressed a clear question and was supported by appropriate inclusion criteria. Attempts to identify relevant studies were undertaken by searching electronic databases and checking references and relevant journals, but the restriction to including only peer-reviewed papers published in English meant that some relevant studies may have been missed (presence of publication bias was reported). Suitable methods appear to have been employed to reduce the risks of reviewer error and bias for the processes of data extraction and study selection.

The authors did not assess trial quality, so it was difficult to assess the strength of the evidence. Sufficient trial details were provided and appropriate methods were used to pool the data and assess heterogeneity.

In light of the possibility of missing studies and the lack of a trial quality assessment, the authors’ conclusions should be interpreted with caution.

**Implications of the review for practice and research**
**Practice:** The authors stated that the evidence supports the use of terlipressin for hepatorenal syndrome reversal, but that terlipressin use requires careful selection of patients and close clinical surveillance.

**Research:** The authors stated that the optimal dose and duration of terlipressin remains unclear and that the predictors of response have not been adequately investigated. They also stated that large trials are needed to assess the link between terlipressin and survival in patients with hepatorenal syndrome.

**Funding**
Project Glomerulonephritis grant.

**Bibliographic details**

**PubMedID**
19440988

**Original Paper URL**

**Indexing Status**
Subject indexing assigned by NLM

**MeSH**
Albumins /therapeutic use; Evidence-Based Medicine; Female; Hepatorenal Syndrome /drug therapy /mortality
AccessionNumber
12009109564

Date bibliographic record published
13/01/2010

Date abstract record published
14/04/2010

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.