
Meta-analysis: terlipressin therapy for the hepatorenal syndrome

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CRD summary

This review assessed the safety and efficacy of terlipressin therapy in patients with hepatorenal syndrome. The authors concluded that terlipressin significantly improves the management of hepatorenal syndrome, but relapse following treatment withdrawal is high. Given the small sample sizes, and the absence of study quality assessment, the extent to which the authors' conclusions are reliable is unclear.

Authors' objectives

To assess the safety and efficacy of terlipressin in patients with hepatorenal syndrome.

Searching

MEDLINE, EMBASE, Current Contents and the Cochrane Library were searched from 1990 to June 2005 for relevant articles. Search terms were reported. This was supplemented by manual searches of selected journals and the reference lists from reviews and clinical trials. The authors stated that several strategies were employed to identify unpublished studies (details were not given). Only English language articles were eligible for inclusion in the review.

Study selection

Clinical trials, including cohort designs, randomised controlled trials (RCTs), and case control studies evaluating terlipressin therapy in hepatorenal syndrome patients (diagnosed according to International Ascites Club criteria) were eligible for inclusion in the review.

The majority of studies were located in western Europe and included largely male patients (aged between 47 to 60.4 years) with type 1 hepatorenal syndrome. Serum creatinine levels ranged from 2.4 to 3.6 mg/dL. The presence of alcoholic cirrhosis was variable. The majority (82.5%) of patients were treated with terlipressin. Mean treatment doses and duration ranged from 1 mg to 6 mg per day, over two to 26 days. Concomitant plasma expanders were given in more than half of the included studies.

The primary outcome of interest was the rate of responder patients (defined as those with a reversal of hepatorenal syndrome after treatment). The secondary outcome was the frequency of responder patients with recurrence of hepatorenal syndrome after interruption/withdrawal of treatment. Other outcomes of interest were side effects (drop-out rate) and all cause mortality.

Two reviewers selected the studies for inclusion in the review and disagreements were resolved by consensus.

Assessment of study quality

The authors did not state that they assessed validity.

Data extraction

Outcomes were extracted or calculated on an intention-to-treat basis in order to arrive at a summary estimate. The odds ratio (OR) was presented for mortality and in the sub-group analysis of clinical controlled trials. Corresponding 95% confidence intervals (CI) were calculated. Study authors were contacted for additional information where necessary.

Two independent reviewers extracted the data for the review and disagreements were resolved by consensus.

Methods of synthesis

Effect sizes for hepatorenal syndrome reversal and drop-out rates were calculated in a random-effects meta-analysis (DerSimonian and Laird) using some method of weighting. Heterogeneity was assessed by the Cochrane Q test and I^2 statistic. Spearman's correlation coefficients were used to explore the potential effects of study and patient variables. Sensitivity analysis was performed using a fixed-effect model to explore subgroups of: trials with type 1 hepatorenal

syndrome patients only; trials from Europe; trials using concomitant plasma expanders; and by study design. Publication bias was reported to be assessed using a funnel plot.

Results of the review

Ten clinical trials (n=154) were included in the review. There were eight cohort studies (n=121), of which four were randomised; one double-blind, cross-over randomised trial (n=9), and one single-blind, placebo-controlled randomised trial (n=24).

The pooled rate of responder patients (with reversal of hepatorenal syndrome after treatment with terlipressin) was positive and statistically significant, 0.52 (95% CI: 0.42, 0.61, $p = 0.00001$, 11 trials, n=154), with no significant heterogeneity between the studies. The pooled frequency of responder patients (with hepatorenal syndrome recurrence after terlipressin withdrawal) was 0.55 (95% CI: 0.40, 0.69, $p = 0.00001$, 6 trials, n=74). Heterogeneity was reported ($I^2 = 44.3%$) but no significant predictive variables were evident. A statistically significant pooled effect on mortality was reported in hepatorenal syndrome patients who were not responders to therapy compared with those who were, OR 5.746 (95% CI: 1.5, 21.9, five trials, n=93).

All sensitivity analyses showed statistically significant improvements in hepatorenal syndrome reversal following terlipressin use. The treatment was well-tolerated and no long term side effects were reported.

Authors' conclusions

Terlipressin can have a significant improvement in the management of hepatorenal syndrome. However, the relapse rate was high in responder patients following treatment withdrawal.

CRD commentary

This review addressed a clear question and was supported by detailed inclusion criteria. A comprehensive database and manual search strategy was performed. The restriction to English language articles means that relevant studies may have been missed and language bias introduced. Although there was some inclusion of theoretically well-designed studies, the absence of a formal validity assessment means that the reliability of included studies and their subsequent synthesis cannot be verified. The review process appeared to be conducted with reasonable rigour. Comprehensive study details were provided but there appeared to be some discrepancies in the reporting of results. Given the variability amongst some of the included studies, the chosen methods of synthesis were appropriate and sensitivity analyses were carried out. The authors' conclusions reflected the evidence presented but, given the small number of included patients and the absence of study quality assessment, the extent to which these conclusions are reliable is unclear.

Implications of the review for practice and research

Practice: The authors did not state any implications for practice.

Research: The authors stated that a large prospective randomised trial is needed to test the efficacy of terlipressin on post liver transplantation outcome, comparing control hepatorenal syndrome patients treated before liver transplantation with those not receiving terlipressin before liver transplantation.

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