Terlipressin for hepatorenal syndrome (Review)

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[Intervention Review]

Terlipressin for hepatorenal syndrome

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ABSTRACT

Background

Clinical trials suggest that terlipressin improves renal function in hepatorenal syndrome, but the evidence concerning mortality is equivocal.

Objectives

To assess the beneficial and harmful effects of terlipressin alone or with albumin versus placebo, no intervention or albumin for hepatorenal syndrome.

Search methods

Eligible trials were identified through electronic (*The Cochrane Library*, MEDLINE, EMBASE and Science Citation Index databases) and manual searches until January 2012.

Selection criteria

Randomised clinical trials involving patients with type 1 or type 2 hepatorenal syndrome were included irrespective of publication status or language.

Data collection and analysis

The review authors independently extracted data from trial reports and undertook correspondence with the authors. Primary outcome measures included mortality, reversal of hepatorenal syndrome and adverse events. Intention-to-treat, random-effects model meta-analyses were performed and results were expressed as risk ratios (RR) with 95% confidence intervals (CI), and the I^2 statistic provided a measure of intertrial heterogeneity. Subgroup, sensitivity, regression and sequential analyses were performed.

Main results

We identified six randomised clinical trials. All had high risk of bias. Five trials assessed terlipressin (with albumin in three trials) versus no intervention (with albumin in three trials) and one trial assessed terlipressin versus albumin. Data from five randomised trials on terlipressin alone (one trial) or terlipressin and albumin (four trials) were included in the review. In total, 74 of 155 (47.7%) patients randomised to terlipressin alone or terlipressin with albumin versus 98 of 154 (63.6%) patients randomised to no intervention, placebo

or albumin died. Random-effects model meta-analysis found that terlipressin reduced mortality (RR 0.76, 95% CI 0.61 to 0.95). The results were stable when repeated with trials on terlipressin plus albumin, trials on patients with type 2 hepatorenal syndrome, and trials with a low risk of selection bias. No evidence of bias or small study effects were identified in regression analyses. In a trial sequential analysis on mortality, the cumulative Z curve approached but did not cross the monitoring boundary suggesting that the results were not stable to adjustment for sparse data and multiple comparisons. Analyses of the remaining outcome measures found that terlipressin and albumin increased the number of patients with reversal of hepatorenal syndrome as well as adverse events, including cardiovascular and gastrointestinal symptoms.

Authors' conclusions

Terlipressin may reduce mortality and improve renal function in patients with type 1 hepatorenal syndrome. Whether the evidence is strong enough to support the intervention for clinical practice could be debated due to the results of the trial sequential analyses. However, the outcome measures assessed are objective, which reduces the risk of bias.

PLAIN LANGUAGE SUMMARY

Terlipressin for patients with hepatorenal syndrome

Patients with severe cirrhosis of the liver may develop kidney failure. The disease is known as hepatorenal (liver-kidney) syndrome. The syndrome is divided into two types, type 1 has a rapid course of the disease whereas type 2 has a more protracted course. The disease may develop as a consequence of the circulatory changes that are associated with cirrhosis. Untreated, the disease is associated with high mortality. The median survival ranges between two weeks to six months. Terlipressin is a drug that affects the circulation and may help reverse the circulatory changes that lead to hepatorenal syndrome.

The present review includes data from five randomised trials on terlipressin alone or with placebo, no intervention or albumin. Our analyses suggest that terlipressin with albumin reduces mortality and improves renal function. The intervention increases the risk of adverse events.

BACKGROUND

Description of the condition

Hepatorenal syndrome is a potentially reversible renal failure associated with severe liver disease (Arroyo 1996). The disease is relatively common among patients with decompensated cirrhosis. In a cohort study of 234 non-azotaemic patients with cirrhosis and ascites, 18% developed hepatorenal syndrome after one year (Gines 1993). The diagnosis includes cirrhosis and ascites plus impaired renal function after exclusion of parenchymal renal disease and factors that may precipitate renal dysfunction in cirrhosis (Salerno 2007). Hepatorenal syndrome is divided into two types with type 1 having the most rapid course of development. Without treatment, type 1 has a median survival of about two weeks and type 2 a median survival of about six months (Arroyo 1996; Gines 2003; Salerno 2007).

Description of the intervention

The development of hepatorenal syndrome has been associated with the circulatory changes seen in cirrhosis of the liver subsequent to portal hypertension and vasodilation of the splanchnic arteries (Cardenas 2003). The vasodilation results in effective underfilling of the renal arteries and activation of the renin-angiotensin-aldosterone, the arginine-vasopressin, and the sympathetic nervous systems (Pasqualetti 1998; Moller 2004; Ruiz del Arbol 2005). Activation of these systems may in turn lead to severe vasoconstriction of the renal arteries and hepatorenal syndrome (Cardenas 2003). The process may be reversed by vasoactive drugs that increase the splanchnic arterial tone. Vasopressin was evaluated initially but was abandoned as it led to severe ischaemias of the mesenteric mucosa, skin and myocardium (Obritsch 2004). Terlipressin is a vasopressin analogue which was introduced as a safer alternative (Freeman 1982). Subsequent studies have evaluated the effects of the somatostatin analogue octreotide and similar vasoconstrictors (Arroyo 2000). The initial trials on terlipressin

were small and some used a cross-over design with a short treatment duration and length of follow-up (Hadengue 1998; Solanki 2003). Subsequent trials have been larger but did not find convincing effects on clinical outcome measures (Martín-Llahí 2008; Neri 2008; Sanyal 2008).

Why it is important to do this review

Meta-analyses on terlipressin for hepatorenal syndrome have been conducted but with equivocal findings (Fabrizi 2009; Dobre 2010; Sagi 2010). Since large randomised trials were published after our previous review (Cochrane 2006), we performed the present systematic review with an update of the available evidence.

OBJECTIVES

The primary objective was to assess the beneficial and harmful effects of terlipressin for hepatorenal syndrome.

METHODS

Criteria for considering studies for this review

Types of studies

Randomised trials were included irrespective of blinding, publication status or language. Trials using a cross-over design were included if data from the first period could be obtained.

Types of participants

Patients described as having type 1 or type 2 hepatorenal syndrome were included.

Types of interventions

The analyses included comparisons of terlipressin alone or with albumin versus placebo, no intervention or albumin.

Types of outcome measures

Based on the guidelines of the Cochrane Hepato-Biliary Group (CHBG), all outcome measures were were classed as primary outcomes. Furthermore, quality of life was added as an outcome measure.

Primary outcomes

Based on the Cochrane Hepato-Biliary Group guidelines and peer review comments, all outcome measures were classed as primary.

- Mortality (all-cause)
- Morbidity: reversal of hepatorenal syndrome and improved renal function as defined by the authors of included trials
- Quality of life
- Adverse events

Search methods for identification of studies

Electronic searches

Electronic searches were performed in *The Cochrane Library*, MEDLINE, EMBASE and Web of Science (Appendix 1).

Searching other resources

Manual searches included scanning of reference lists in relevant articles and conference proceedings. Additional ongoing or unpublished trials were identified through searches of trial registers through the World Health Organization (WHO) Clinical Trials Registry Platform search portal (http://apps.who.int/trialsearch/).

Data collection and analysis

Selection of studies

Two authors (LG and AK) independently selected trials eligible for inclusion from the updated literature searches. Excluded trials were listed with the reasons for exclusion.

Data extraction and management

Review authors independently extracted data (LG and AK). All disagreements were resolved through discussion. We wrote to authors of the included trials to obtain additional information not described in the published reports.

Assessment of risk of bias in included studies

The allocation methods were extracted as the primary methods of bias control (Wood 2008). The assessment included the allocation sequence generation (classed as low risk of bias if based on a table of random numbers, computer generated random numbers or similar) and the allocation concealment (classed as low risk of bias if patients were randomised through a central independent unit, serially numbered opaque sealed envelopes or similar). We also assessed whether trials were described as double blind and the

method of blinding (with double blind placebo controlled trials classed as low risk of bias), whether incomplete outcome data were addressed (classed as low risk of bias if all patients were accounted for in the report and analysis), whether the clinically relevant outcome measures were defined and reported (selective reporting), and other potential biases including sample size calculations and whether the trial was terminated early or was prolonged. For trials terminated early, we recorded whether this was based on predefined criteria.

Measures of treatment effect

All outcome measures were dichotomous and were expressed using relative risks (RR) with 95% confidence intervals (CI).

Unit of analysis issues

Since our primary outcome measure was mortality, and since hepatorenal syndrome is a disease with a fluctuating course, we only planned to include data from the first treatment period of cross-over trials, if any had been identified.

Dealing with missing data

Data were sought on all patients randomised to allow intention-to-treat analyses. For patients with missing outcome data, carry forward of the last observed response was used.

Assessment of heterogeneity

Intertrial heterogeneity was expressed using the I^2 statistic.

Assessment of reporting biases

Evidence of reporting bias was assessed as described above. We also planned to compare outcome measures described in protocols and published reports, if any protocols had been available.

Data synthesis

The analyses were performed using the statistical programs RevMan 5 (RevMan), STATA (STATA) and TSA (TSA 2008). All meta-analyses were performed using random-effects models due to expected clinical heterogeneity (based on patient inclusion criteria and treatment dose plus duration).

Subgroup analysis and investigation of heterogeneity

For all-cause mortality, we performed subgroup regression and sequential analyses to evaluate sources of intertrial heterogeneity, bias, small study effects and errors associated with cumulative testing (Higgins 2011).

In the subgroup analyses, we analysed the effect of the intervention when including only:

- trials on type 1 hepatorenal syndrome;
- trials on terlipressin with albumin;
- trials with a low risk of selection bias based on the assessment of allocation methods.

The risk of small study effects was assessed through regression analyses (Egger's test).
Sequential analyses were performed using the monitoring boundaries approach (Wetterslev 2008; Higgins 2011). The analysis was performed with alpha set to 5%, power to 80%, model-based heterogeneity, and including the control event proportion and intervention effects observed in the meta-analysis. The effect measure was relative risk (random-effects model), the relative risk reduction 25% (low bias based), incidence in the control arm of 76%, and heterogeneity correction 47%.

Sensitivity analysis

The sensitivity and subgroup analyses included repetitive meta-analyses using a fixed-effect model to afford less weight to smaller trials.

RESULTS

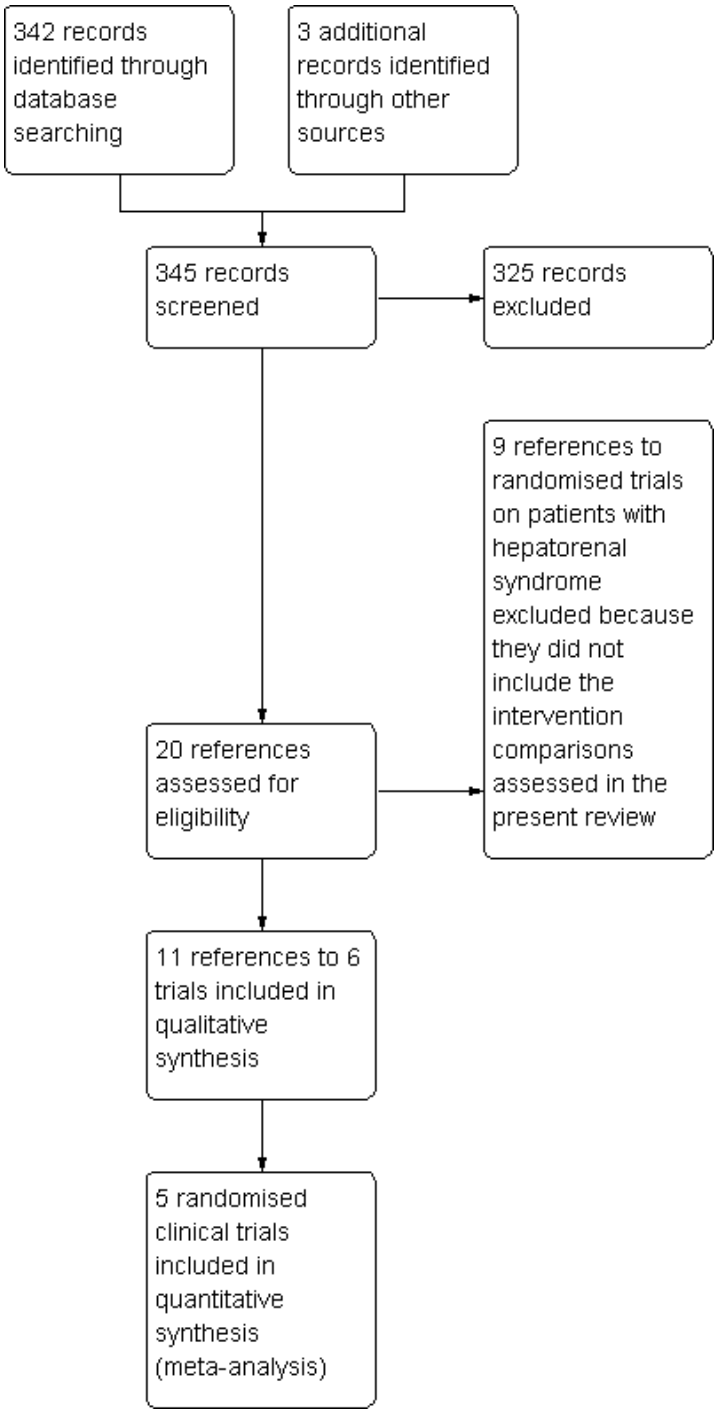
Description of studies

See: Characteristics of included studies; Characteristics of excluded studies; Characteristics of ongoing studies.

Results of the search

After scanning the 345 potentially eligible references identified in the literature searches (Appendix 1), 20 references referred to trials that were potentially eligible for inclusion (Figure 1). Among these, nine that referred to randomised trials on patients with hepatorenal syndrome had to be excluded because they did not evaluate the interventions assessed in the present review. The remaining 11 references referred to six randomised trials that fulfilled our inclusion criteria (Hadengue 1998; Yang 2001; Solanki 2003; Martín-Llahí 2008; Neri 2008; Sanyal 2008). One trial used a cross-over design (Hadengue 1998). We were unable to retrieve data from the first period of the trial. Accordingly, the trial could not be included in our quantitative analyses. Since no data were included from the cross-over trial, the trial is not included in the description of included studies.

Figure 1. Study flow diagram.



Included studies

Trial characteristics

All trials were published as full paper articles (Characteristics of included studies). One trial was translated from Chinese (Yang 2001). The remaining trials were published in English. The trials were conducted in the United States, Italy, Spain, Canada, India, China, Germany and Russia. All trials were performed in specialised units in an intensive or semi-intensive setting. Two trials were multicentred and three were single centre trials. The included patients were followed for six months in one trial (Sanyal 2008)and to the end of treatment in four trials. None of the included trials assessed health economics.

Patient characteristics

Hepatorenal syndrome was diagnosed based on evidence of cirrhosis, serum creatinine more than 133 µmol/L (1.5 mg/dL) after diuretic withdrawal and volume expansion plus absence of shock, ongoing infections, parenchymal renal disease, and treatment with nephrotoxic drugs. In one trial (Martín-Llahí 2008) patients were diagnosed as having type 2 hepatorenal syndrome based on a serum creatinine more than 175 µmol/L (1.97 mg/dl) and absence of bacterial infection associated with findings of a systemic inflammatory response. In the remaining trials the type of hepatorenal syndrome was diagnosed based on the course of the disease, with type 1 developing within two weeks (Arroyo 1996). One trial did not report the proportion of patients with type 1 hepatorenal syndrome (Yang 2001). In one trial (Martín-Llahí 2008), 56% of patients had type 1 and 44% had type 2 hepatorenal syndrome. In remaining trials, all patients had type 1 hepatorenal syndrome at baseline. The mean age in the treatment and control groups ranged from 51 to 59 years and 52 to 60 years, respectively, The proportion of men ranged from 40% to 71% and the proportion with alcoholic liver disease from 13% to 72%.

Intervention characteristics

The median initial dose of terlipressin was 1 mg four times daily. In two trials (Yang 2001; Solanki 2003) the dose of terlipressin was not adjusted. In the remaining trials, the dose of terlipressin was increased to 2 mg four to six times daily after three days in the non-responders (patients without improved renal function). One trial assessed terlipressin versus no intervention (Yang 2001); one trial assessed terlipressin versus placebo (Hadengue 1998); one trial assessed terlipressin versus albumin (Neri 2008); and three trials assessed terlipressin plus albumin verus albumin (Solanki 2003; Martín-Llahí 2008; Sanyal 2008). Accordingly, five trials assessed terlipressin versus no intervention or placebo (Hadengue 1998; Yang 2001; Solanki 2003; Martín-Llahí 2008; Sanyal 2008). Of the former five trials, three used albumin both in the experimental group and in the control group.

Excluded studies

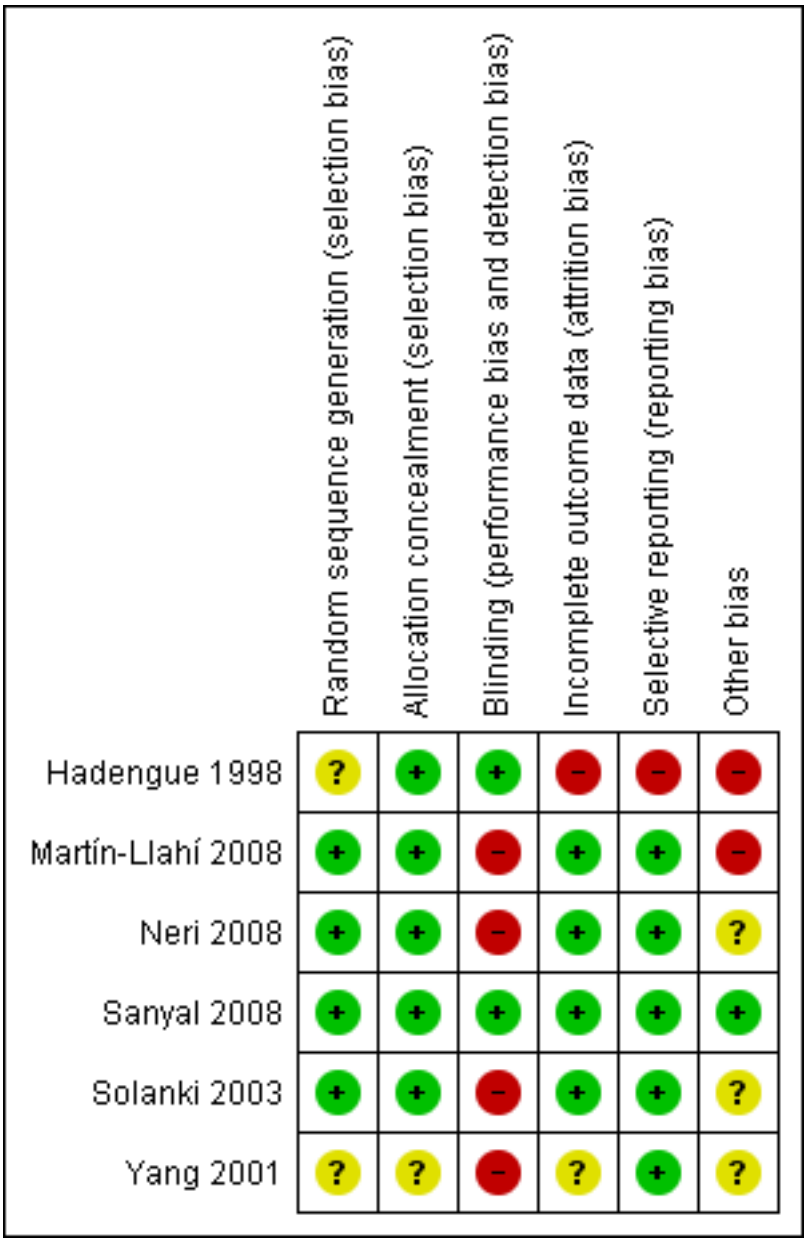
None of the excluded trials assessed the interventions specified for the present review. The excluded trials compared terlipressin and albumin versus other vasoactive drugs for hepatorenal syndrome (Excluded studies).

Risk of bias in included studies

Allocation

One trial did not report the allocation methods. This trial was classed as having unclear control of selection bias (Figure 2). The remaining trials reported adequate allocation and were classed as having a low risk of selection bias.

Figure 2. Methodological quality summary: review authors' judgments about each methodological quality item for each included study.



Blinding

One trial reported double blinding of patients and investigators by use of a placebo infusion (Figure 2). One trial was described as single blind. The trial did not specify whether blinding was maintained for patients, investigators, or other persons involved in the trial. Four trials were conducted without blinding.

Incomplete outcome data

Three trials reported dropouts and withdrawals and included all patients in intention-to-treat analyses (Martín-Llahí 2008; Neri 2008; Sanyal 2008). One trial followed patients to the end of treatment but obtained additional follow-up data for some of the included patients (Solanki 2003). The strategy for obtaining additional information and the number of patients without additional follow-up data was not reported. In the remaining trials, no losses to follow-up were reported.

Selective reporting

All trials reported clinically relevant outcome measures.

Other potential sources of bias

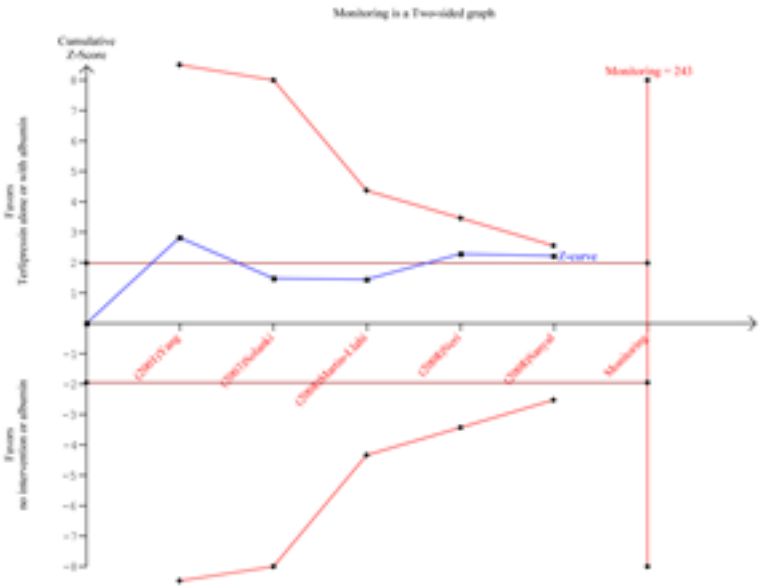
One trial reported sample size calculations and achieved the required sample size (Sanyal 2008). One trial was terminated prematurely due to unexpectedly low event rates (Martín-Llahí 2008). The remaining trials did not report sample size calculations or whether the trials were terminated early.

Effects of interventions

Mortality

Random-effects model meta-analysis found that terlipressin, alone or with albumin, reduced mortality compared with no intervention, placebo or albumin (RR 0.75, 95% CI 0.59 to 0.97; I^2 39%; Analysis 1.1). The effect was also seen when the analysis was limited to trials on patients with type 1 hepatorenal syndrome (Analysis 1.5), trials on terlipressin and albumin (Analysis 1.6), and trials with a low risk of selection bias (Analysis 1.7). Regression analysis showed no evidence of bias (P = 0.224). In trial sequential analysis, the cumulative Z curve approached but did not cross the monitoring boundary suggesting that the results were not stable to adjustments for sparse data and multiple testing (Figure 3). A fixed-effect model meta-analysis found that terlipressin plus albumin reduced mortality compared with no intervention or albumin (RR 0.76, 95% CI 0.63 to 0.91; Analysis 1.8).

Figure 3. Trial sequential analysis of terlipressin versus no intervention on mortality in patients with hepatorenal syndrome. The required information size was calculated to 466 participants based upon a control group mortality of 76%; a relative risk reduction of 25%; an alpha of 5%; and a beta of 20%. The blue cumulative Z curve crosses the conventional alpha of P = 0.05 twice, but not the trial sequential alpha-spending monitoring boundaries (inward sloping red lines).



Reversal of hepatorenal syndrome

All trials reporting the number of patients with reversal of hepatorenal syndrome and improved renal function assessed terlipressin and albumin versus albumin (Analysis 1.2). Random-effects model meta-analysis showed that terlipressin had a beneficial effect on this outcome measure.

Quality of life

None of the included trials assessed the quality of life.

Adverse events

Terlipressin also increased the risk of cardiovascular adverse events (RR 7.26, 95% CI 1.70 to 31.05; I^2 = 0%; Analysis 1.4). The remaining adverse events included abdominal pain, diarrhoea, bacterial infections, chest pain, circulatory overload, gastrointestinal bleeding, hepatic encephalopathy, livedo reticularis, respiratory distress or acidosis and did not appear to differ between the intervention and control groups.

DISCUSSION

Summary of main results

The present review suggests that terlipressin may reduce mortality and have a beneficial effect on renal function in type 1 hepatorenal syndrome. However, most of the patients were only followed to the end of treatment and there are few available data on adverse events. Accordingly, the prognosis of the underlying liver disease should be considered in treatment decisions.

The evidence on the use of terlipressin alone and intervention benefits in type 2 hepatorenal syndrome were scarce. Only one of the included trials assessed terlipressin alone (Yang 2001). The trial was small and the findings were inconclusive. Likewise, only one of the trials on terlipressin and albumin versus albumin included patients with type 2 hepatorenal syndrome (Martín-Llahí 2008). The number of patients with type 2 hepatorenal syndrome included in the trial was relatively small. Accordingly, no clear intervention effects were identified for this patient group. There was, however, clear evidence suggesting that treatment with terlipressin is associated with a number of adverse events. In particular, the intervention seems to increase the risk of cardiovascular adverse events, some of which may be potentially serious. Other patient reports also show that terlipressin may be associated with severe

adverse effects (Shawcross 2004; Krag 2008). The intervention should, therefore, be closely monitored.

The present review includes three small trials comparing terlipressin plus albumin versus albumin alone, in different dosing regimens (continuous versus bolus administration). The fact that no clear intervention effects were identified may reflect that the reported results were interim analyses of part of the planned patient cohort, although this was not specifically stated. We also identified three trials assessing terlipressin versus noradrenaline (Alessandria 2007a; Angeli 2008a; Sharma 2008a). The trials on terlipressin versus noradrenaline also found no clear differences between the intervention groups. The trials did not report sample size calculations but, based on the number of patients included, the trials were not designed to establish equivalence. Additional evidence is needed to reassess the results.

Overall completeness and applicability of evidence

We found little evidence of clinical intertrial heterogeneity. The mean control group Child-Pugh scores were remarkably similar (11 in three trials (Martín-Llahí 2008; Neri 2008; Sanyal 2008)). Likewise, the included trials on terlipressin and albumin used similar criteria to diagnose hepatorenal syndrome, based on previous recommendations (Arroyo 1996). The current diagnostic criteria include presence of cirrhosis, ascites, elevated serum creatinine after at least 48 hours of diuretic withdrawal and volume expansion combined with absence of shock, treatment with nephrotoxic drugs, and parenchymal renal disease (Salerno 2007). The use of minor criteria and exclusion of patients with infections is now omitted from the criteria. Type 1 hepatorenal syndrome is now defined as renal failure with serum creatinine increasing to 226 µmol/L (2.5 mg/dL) within two weeks. Type 2 hepatorenal syndrome is defined as a moderate to slowly progressive renal failure with serum creatinine between 133 and 226 µmol/L (1.5 to 2.5 mg/dL). Although the included trials used previously established criteria, the evidence is likely to be applicable today. It may, however, be argued that there is still room for trials on terlipressin and albumin using the current diagnostic criteria.

The duration of the effect of terlipressin on mortality should be considered when deciding whether or not to treat a patient with hepatorenal syndrome (Gluud 2010). Some patients may die in spite of a clear improvement in renal function (Martín-Llahí 2008; Sanyal 2008). After an initial complete normalisation of renal function, hepatorenal syndrome may reappear. We attempted to perform a post hoc analysis to determine the effect of treatment on recurrence of hepatorenal syndrome but we were unable to extract the necessary data.

Quality of the evidence

The present review identified a number of methodological concerns, including unclear randomisation, lack of sample size calculations and lack of blinding. Previous meta-epidemiological studies show that allocation concealment is one of the most important predictors of bias control (Wood 2008). The allocation sequence generation and allocation concealment were classed as adequate in all trials on terlipressin and albumin versus albumin. Excluding the trial without adequate randomisation had no influence on the overall results.

Another potential source of bias in included trials was related to the lack of reported sample size calculations. For the trials without sample size calculations, we were unable to determine whether the trials were terminated prematurely, terminated at an arbitrary point, or extended due to low event rates. One of the included trials reporting sample size calculations had to be terminated prematurely due to unexpectedly low event rates (Martín-Llahí 2008). The trial assessed terlipressin plus albumin versus albumin and was terminated after an interim analysis suggested that 2000 patients would be required to achieve sufficient statistical power. Whether the interim results reflect a true (low) intervention effect, a random error, or the inclusion criteria is difficult to assess. One possible explanation could be that a number of the included patients had type 2 hepatorenal syndrome. Overall, there is little evidence on this latter patient group.

Potential biases in the review process

One of the main limitations of the present review is related to the relatively low overall sample size. Identification of patients who clearly fulfil the diagnostic criteria for hepatorenal syndrome may be difficult, as is the recruitment of critically ill patients in clinical trials. Accordingly, the largest trials were multicentred and multinational (Sanyal 2008). This involvement of several clinical sites in more than one geographical region increases the clinical heterogeneity. On the other hand, the heterogeneity also increases the external validity, making it possible to extrapolate the results to larger patient populations in similar specialised centres. The heterogeneity increases the need for additional subgroup and sensitivity analyses. Analysis of individual patient data would have increased the possibilities of performing such analyses. Unfortunately, we were not able to conduct individual patient data meta-analyses, and we were only able to perform a few additional analyses to explore sources of intertrial heterogeneity due to the limited number of included trials.

Agreements and disagreements with other studies or reviews

Three of the included trials found that baseline serum creatinine was an independent predictor of survival (Martín-Llahí 2008; Neri 2008; Sanyal 2008). In our analyses, the baseline creatinine in the

control groups of the trials on terlipressin plus albumin ranged from 194 to 362 µmol/L (2.2 to 4.1 mg/dL). All trials found similar baseline values for the treatment and control groups. In agreement with previous findings, our analyses suggest that the treatment effect was the largest in the trial with the lowest baseline serum creatinine (Solanki 2003). This may suggest that treatment should be administered early and that a protracted deterioration in renal function impedes recovery.

A number of meta-analyses have assessed the effect of terlipressin for hepatorenal syndrome (Fabrizi 2009; Dobre 2010; Sagi 2010). The results concerning mortality are equivocal. In agreement with our findings, one meta-analysis found that terlipressin increases survival among patients with type 1 hepatorenal syndrome (Sagi 2010). The two remaining meta-analyses found no clear effect of terlipressin on survival, although only one performed a meta-analysis addressing this question (Fabrizi 2009). In agreement with our findings, all reviews found that terlipressin improves renal function but also increases the risk of cardiovascular and ischaemic adverse events. The differences between the conclusions in the different reviews are mainly related to the inclusion criteria. For example, one review only included placebo controlled trials (Fabrizi 2009). This decision is not clearly supported by previous evidence on the importance of bias control in randomised trials (Gluud 2006; Wood 2008). Although lack of blinding may affect the risk of bias, there is no clear or consistent evidence to support the exclusion of open trials from meta-analyses since the effect of blinding is inconsistent across trials. The extent as well as the effect of bias associated with lack of blinding is unpredictable and does not support the a priori exclusion of trials based on this component alone.

AUTHORS' CONCLUSIONS

Implications for practice

The combined evidence suggests that terlipressin may be considered for patients with type 1 hepatorenal syndrome.

Implications for research

Additional research may be needed to assess the effect of terlipressin for hepatorenal syndrome that is m identified by the updated diagnostic criteria. Future trials may need to be planned at a multinational level since inclusion of a sufficient number of patients may otherwise prove difficult.

ACKNOWLEDGEMENTS

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Contact Editors: Gennaro D'Amico, Italy; Ronald L Koretz, USA; Christian Gluud, Denmark.

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* *Indicates the major publication for the study*

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Hadengue 1998

Methods	- Single centre trial.
Participants	- Mean age • terlipressin group 53 years. • placebo group 53 years. - Proportion of men 56%. - Proportion with alcoholic liver disease 78%.
Interventions	Terlipressin • 1 mg twice daily for two days.
Outcomes	- Duration of follow-up: end of treatment.
Country of origin	France.
Interventions	Terlipressin versus placebo.
Proportion with type 1 hepatorenal syndrome	100%
Notes	Cross-over trial. The trial does not report outcome measures for the first period. The trial is therefore not included in our quantitative analyses

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not described.
Allocation concealment (selection bias)	Low risk	Identical coded drug containers.
Blinding (performance bias and detection bias) All outcomes	Low risk	Double blinding achieved using terlipressin placebo.
Incomplete outcome data (attrition bias) All outcomes	High risk	Clinical outcome measures are not reported according to the intervention group or treatment period. Three patients were withdrawn and excluded from the analyses
Selective reporting (reporting bias)	High risk	Clinical outcome measures not accounted for.

Hadengue 1998 (*Continued*)

Other bias	High risk	Sample size calculation not reported.

Martín-Llahí 2008

Methods	- Multicentre trial.
Participants	Mean age • terlipressin plus albumin group 59 years. • albumin group 52 years. - Proportion of men 63%. - Proportion with alcoholic liver disease 72%.
Interventions	Terlipressin • 1 mg six times daily. If no improvement in renal function was observed, the dose was increased to 2 mg six times daily. Albumin • 1 g/kg for 24 hours then 40 g/day adjusted according to the central venous pressure.
Outcomes	- Duration of follow-up: 3 months after treatment.
Country of origin	Spain.
Interventions	Terlipressin plus albumin versus albumin for a maximum of 15 days
Proportion with type 1 hepatorenal syndrome	56%
Notes	Full paper article.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Computer generated random numbers.
Allocation concealment (selection bias)	Low risk	Central randomisation.
Blinding (performance bias and detection bias) All outcomes	High risk	Open trial.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Intention-to-treat analyses with all patients randomised reported

Selective reporting (reporting bias)	Low risk	Clinically relevant outcome measures reported. Primary outcome measures • mortality after three months and • improvement in renal function.
Other bias	High risk	- Sample size calculations performed. The trial was terminated after a preliminary analysis suggested that the event rate was considerably lower than expected

Neri 2008

Methods	- Multicentre trial.
Participants	Mean age • terlipressin group 59 years • albumin group 60 years. - Proportion of men 40%. - Proportion with alcoholic liver disease 13%.
Interventions	Terlipressin • 1 mg four times daily for 5 days then 0.5 mg four times/day for 14 days. Albumin • 1 g/kg for 24 hours then 40 to 80 g/day.
Outcomes	- Duration of follow-up: six months after hospital discharge
Country of origin	Italy.
Interventions	Terlipressin plus albumin versus albumin for 19 days.
Proportion with type 1 hepatorenal syndrome	100%
Notes	- Patients with recurrence of hepatorenal syndrome after the initial treatment were treated with terlipressin plus albumin

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Computer generated list of random numbers.
Allocation concealment (selection bias)	Low risk	Central randomisation.
Blinding (performance bias and detection bias) All outcomes	High risk	Open trial.

Neri 2008 (*Continued*)

Incomplete outcome data (attrition bias) All outcomes	Low risk	No losses to follow-up reported.
Selective reporting (reporting bias)	Low risk	Clinically relevant outcome measures reported. Primary outcome measure • Resolution of hepatorenal syndrome defined as normalisation of creatinine.
Other bias	Unclear risk	Sample size calculation not reported.

Sanyal 2008

Methods	- Multicentre trial.
Participants	Mean age • terlipressin plus albumin group 51 years. • albumin group 53 years. - Proportion of men 71%. - Proportion with alcoholic liver disease 36%.
Interventions	Terlipressin • 1 mg four times daily increased to 2 mg four times daily if serum creatinine was not decreased by at least 30% Albumin • 100 g for 24 hours then 25 g daily.
Outcomes	Follow-up: 6 months.
Country of origin	United States, Germany, and Russia.
Interventions	Terlipressin plus albumin versus albumin for a maximum of 14 days
Proportion with type 1 hepatorenal syndrome	100%
Notes	- Full paper article.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Computer generated random numbers.
Allocation concealment (selection bias)	Low risk	Central randomisation.

Sanyal 2008 (*Continued*)

Blinding (performance bias and detection bias) All outcomes	Low risk	Double blind using terlipressin placebo.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Intention-to-treat analyses including all patients randomised are reported
Selective reporting (reporting bias)	Low risk	Clinically relevant outcome measures reported. Primary outcome measure • treatment success at day 14 defined as normalisation of serum creatinine on 2 measurements with at least 48 hour intervals and no dialysis, death, or recurrence of HRS type 1 before day 15.
Other bias	Low risk	Sample size calculation reported and preset sample size achieved

Solanki 2003

Methods	- Single centre trial.
Participants	Mean age • terlipressin and albumin group 51 years. • albumin group 52 years. - Proportion of men 71%. - Proportion with alcoholic liver disease 33%.
Interventions	Terlipressin • 1 mg twice daily. Albumin • 20 g daily.
Outcomes	- Duration of follow-up: end of treatment.
Country of origin	India.
Interventions	Terlipressin plus albumin versus placebo plus albumin for 15 days
Proportion with type 1 hepatorenal syndrome	100%
Notes	Full paper article.
Risk of bias	

Bias	**Authors' judgement**	**Support for judgement**

Solanki 2003 (*Continued*)

Random sequence generation (selection bias)	Low risk	Random number table
Allocation concealment (selection bias)	Low risk	Centralised randomisation through an independent statistician
Blinding (performance bias and detection bias) All outcomes	High risk	The trial is described as single blind, but whether the patient or investigators were blinded is not described
Incomplete outcome data (attrition bias) All outcomes	Low risk	There were no losses to follow-up.
Selective reporting (reporting bias)	Low risk	Clinically relevant outcome measures reported.
Other bias	Unclear risk	Sample size calculation: not reported.

Yang 2001

Methods	Single centre trial.
Participants	Patient characteristics not reported.
Interventions	Terlipressin • 1 mg twice daily.
Outcomes	- Duration of follow-up 15 days.
Country of origin	China.
Interventions	Terlipressin versus no intervention for 15 days.
Proportion with type 1 hepatorenal syndrome	Not reported.
Notes	Full paper article.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Not described.
Allocation concealment (selection bias)	Unclear risk	Not described.

Yang 2001 (*Continued*)

Blinding (performance bias and detection bias) All outcomes	High risk	Open trial.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Unclear reporting of losses to follow-up.
Selective reporting (reporting bias)	Low risk	Clinically relevant outcome measures reported.
Other bias	Unclear risk	Sample size calculations are not reported.

SEM = standard error of mean.
g = gram.

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Alessandria 2007	Randomised trial on noradrenaline plus albumin versus terlipressin plus albumin for hepatorenal syndrome
Angeli 2008	Randomised trial comparing different modes of administering terlipressin plus albumin for hepatorenal syndrome
Cavalli 2012	Randomised trial on terlipressin and albumin versus midodrine and octreotide and albumin for hepatorenal syndrome
Chelarescu 2003	Randomised trial comparing captopril plus octreotide versus octreotide published in abstract form
Pomier 2003	Cross-over trial on octreotide for hepatorenal syndrome.
Sharma 2008	Randomised trial on noradrenalin plus albumin versus terlipressin plus albumin for hepatorenal syndrome
Silawat 2011	Randomised trial on dopamine versus terlipressin plus albumin for hepatorenal syndrome

Characteristics of ongoing studies *[ordered by study ID]*

NCT00742339

Trial name or title	Terlipressin + albumin versus midodrine + octreotide in the treatment of hepatorenal syndrome
Methods	Randomised trial.
Participants	Patients with type 1 or 2 hepatorenal syndrome.

NCT00742339 (*Continued*)

Interventions	Terlipressin plus albumin versus midodrine plus octreotide.
Outcomes	The primary outcome measure will be normalisation of creatinine at the end of treatment
Starting date	May 2005.
Contact information	Dr Angeli +390498218676 pangeli@unipd.it
Notes	Estimated enrolment 100 patients.

NCT01143246

Trial name or title	A Placebo-Controlled, Double-Blind Study to Confirm the Reversal of Hepatorenal Syndrome Type 1 With Terlipressin
Methods	Study type: interventional. Study design: allocation: randomised. Endpoint classification: safety/efficacy study. Intervention model: parallel assignment. Masking: double blind (subject, investigator). Primary purpose: treatment.
Participants	Cirrhosis, ascites and hepatorenal syndrome type 1.
Interventions	Drug: terlipressin. Blinded terlipressin reconstituted with 5 mL of sterile 0.9% sodium chloride solution for injection will be administered intravenously as a slow bolus injection over 2 minutes at a dose of 1 mg (1 vial) every 6 hours (4 mg/day). Other Name: Lucassin®. Drug: placebo. Lyophilized mannitol reconstituted with 5 mL of sterile 0.9% sodium chloride solution administered intravenously as a slow bolus injection over 2 minutes at a dose of 1 mg (1 vial) every 6 hours (4 mg/day)
Outcomes	Confirmed HRS Reversal: the percentage of subjects with two serum creatinine (SCr) values of $\leq$ 133 µmol/L (1.5 mg/dL) at least 48 hours apart, on treatment, and without intervening RRT or liver transplant
Starting date	September 2010.
Contact information	Diane Stebbins diane.stebbins@ikaria.com
Notes	Estimated enrolment:180

DATA AND ANALYSES

Comparison 1. Terlipressin alone or with albumin versus no intervention or albumin

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Mortality	5	249	Risk Ratio (M-H, Random, 95% CI)	0.75 [0.59, 0.97]
2 Reversal of hepatorenal syndrome	4	234	Risk Ratio (M-H, Random, 95% CI)	3.76 [2.21, 6.39]
3 Improved renal function	4	234	Risk Ratio (M-H, Random, 95% CI)	2.00 [1.11, 3.62]
4 Adverse events	4		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
4.1 Abdominal pain or diarrhoea	2	76	Risk Ratio (M-H, Random, 95% CI)	5.42 [0.66, 44.71]
4.2 Bacterial infection	1	46	Risk Ratio (M-H, Random, 95% CI)	0.75 [0.39, 1.43]
4.3 Cardovascular adverse events	4	234	Risk Ratio (M-H, Random, 95% CI)	7.26 [1.70, 31.05]
4.4 Chest pain	1	52	Risk Ratio (M-H, Random, 95% CI)	5.0 [0.25, 99.34]
4.5 Circulatory overload	1	46	Risk Ratio (M-H, Random, 95% CI)	1.75 [0.59, 5.17]
4.6 Gastrointestinal bleeding	1	46	Risk Ratio (M-H, Random, 95% CI)	0.67 [0.22, 2.05]
4.7 Hepatic encephalopathy	1	46	Risk Ratio (M-H, Random, 95% CI)	1.0 [0.68, 1.47]
4.8 Livedo reticularis	1	112	Risk Ratio (M-H, Random, 95% CI)	3.00 [0.12, 72.10]
4.9 Respiratory distress or acidosis	1	112	Risk Ratio (M-H, Random, 95% CI)	7.0 [0.37, 132.46]
5 Mortality in trials on type 1 hepatorenal syndrome	3	188	Risk Ratio (M-H, Random, 95% CI)	0.71 [0.51, 0.98]
6 Mortality in trials on terlipressin and albumin	4	234	Risk Ratio (M-H, Random, 95% CI)	0.77 [0.61, 0.97]
7 Mortality in trials with a low risk of selection bias	4	234	Risk Ratio (M-H, Random, 95% CI)	0.77 [0.61, 0.97]
8 Mortality analysed using a fixed effect model	5	249	Risk Ratio (M-H, Fixed, 95% CI)	0.76 [0.63, 0.91]

Analysis 1.1. Comparison 1 Terlipressin alone or with albumin versus no intervention or albumin, Outcome 1 Mortality.

Review: Terlipressin for hepatorenal syndrome

Comparison: 1 Terlipressin alone or with albumin versus no intervention or albumin

Outcome: 1 Mortality

Study or subgroup	Treatment n/N	Control n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
Solanki 2003	7/12	12/12		18.5 %	0.60 [0.37, 0.97]
Sanyal 2008	32/56	35/56		30.6 %	0.91 [0.67, 1.24]
Neri 2008	12/26	21/26		19.7 %	0.57 [0.36, 0.90]
Mart n-Llah 2008	17/23	19/23		30.4 %	0.89 [0.66, 1.22]
Yang 2001	0/8	3/7		0.8 %	0.13 [0.01, 2.10]
Total (95% CI)	**125**	**124**		**100.0 %**	**0.75 [0.59, 0.97]**

Total events: 68 (Treatment), 90 (Control)

Heterogeneity: $Tau^2 = 0.03$; $Chi^2 = 6.56$, df = 4 (P = 0.16); $I^2 = 39\%$

Test for overall effect: Z = 2.19 (P = 0.028)

Test for subgroup differences: Not applicable

Analysis 1.2. Comparison 1 Terlipressin alone or with albumin versus no intervention or albumin, Outcome 2 Reversal of hepatorenal syndrome.

Review: Terlipressin for hepatorenal syndrome

Comparison: 1 Terlipressin alone or with albumin versus no intervention or albumin

Outcome: 2 Reversal of hepatorenal syndrome

Study or subgroup	Treatment n/N	Control n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
Mart n-Llah 2008	9/23	1/23		7.2 %	9.00 [1.24, 65.41]
Neri 2008	21/26	5/26		43.1 %	4.20 [1.87, 9.44]
Sanyal 2008	19/56	7/56		46.1 %	2.71 [1.24, 5.94]
Solanki 2003	5/12	0/12		3.6 %	11.00 [0.67, 179.29]
Total (95% CI)	**117**	**117**		**100.0 %**	**3.76 [2.21, 6.39]**

Total events: 54 (Treatment), 13 (Control)

Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 2.12$, df = 3 (P = 0.55); $I^2 = 0.0\%$

Test for overall effect: Z = 4.88 (P < 0.00001)

Test for subgroup differences: Not applicable

Analysis 1.3. Comparison 1 Terlipressin alone or with albumin versus no intervention or albumin, Outcome 3 Improved renal function.

Review: Terlipressin for hepatorenal syndrome

Comparison: 1 Terlipressin alone or with albumin versus no intervention or albumin

Outcome: 3 Improved renal function

Study or subgroup	Treatment n/N	Control n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
Mart n-Llah 2008	10/23	2/23		13.6 %	5.00 [1.23, 20.35]
Neri 2008	25/26	16/26		50.0 %	1.56 [1.14, 2.14]
Sanyal 2008	16/56	10/56		32.2 %	1.60 [0.80, 3.22]
Solanki 2003	5/12	0/12		4.2 %	11.00 [0.67, 179.29]
Total (95% CI)	**117**	**117**		**100.0 %**	**2.00 [1.11, 3.62]**

Total events: 56 (Treatment), 28 (Control)

Heterogeneity: $Tau^2 = 0.16$; $Chi^2 = 5.69$, df = 3 (P = 0.13); $I^2 = 47\%$

Test for overall effect: Z = 2.30 (P = 0.022)

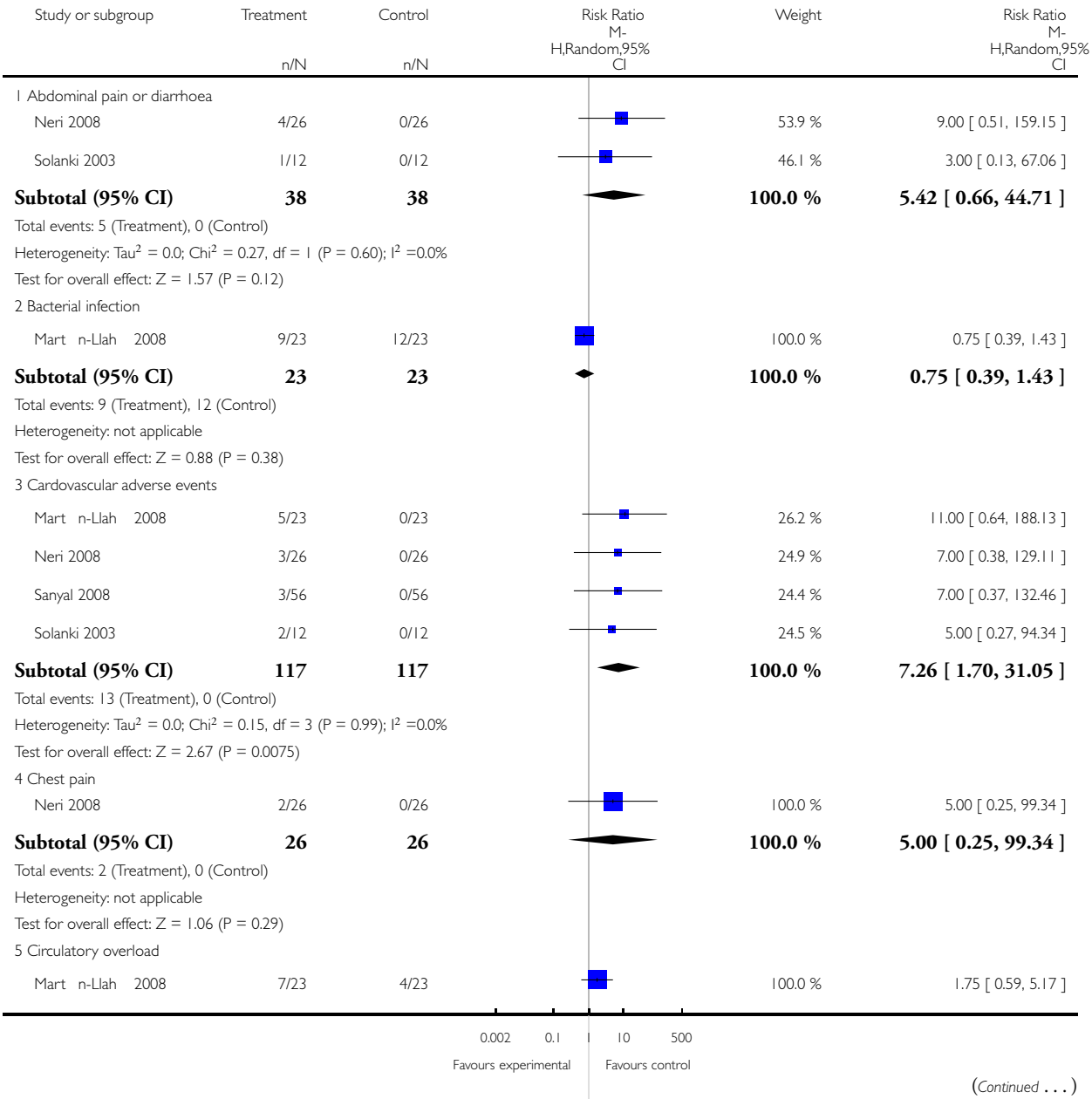
Test for subgroup differences: Not applicable

Analysis 1.4. Comparison 1 Terlipressin alone or with albumin versus no intervention or albumin, Outcome 4 Adverse events.

Review: Terlipressin for hepatorenal syndrome

Comparison: 1 Terlipressin alone or with albumin versus no intervention or albumin

Outcome: 4 Adverse events



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Study or subgroup	Treatment n/N	Control n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
Subtotal (95% CI)	**23**	**23**		**100.0 %**	**1.75 [0.59, 5.17]**
Total events: 7 (Treatment), 4 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.01 (P = 0.31)					
6 Gastrointestinal bleeding					
Mart n-Llah 2008	4/23	6/23		100.0 %	0.67 [0.22, 2.05]
Subtotal (95% CI)	**23**	**23**		**100.0 %**	**0.67 [0.22, 2.05]**
Total events: 4 (Treatment), 6 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.71 (P = 0.48)					
7 Hepatic encephalopathy					
Mart n-Llah 2008	16/23	16/23		100.0 %	1.00 [0.68, 1.47]
Subtotal (95% CI)	**23**	**23**		**100.0 %**	**1.00 [0.68, 1.47]**
Total events: 16 (Treatment), 16 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.0 (P = 1.0)					
8 Livedo reticularis					
Sanyal 2008	1/56	0/56		100.0 %	3.00 [0.12, 72.10]
Subtotal (95% CI)	**56**	**56**		**100.0 %**	**3.00 [0.12, 72.10]**
Total events: 1 (Treatment), 0 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.68 (P = 0.50)					
9 Respiratory distress or acidosis					
Sanyal 2008	3/56	0/56		100.0 %	7.00 [0.37, 132.46]
Subtotal (95% CI)	**56**	**56**		**100.0 %**	**7.00 [0.37, 132.46]**
Total events: 3 (Treatment), 0 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.30 (P = 0.19)					

Analysis 1.5. Comparison 1 Terlipressin alone or with albumin versus no intervention or albumin, Outcome 5 Mortality in trials on type 1 hepatorenal syndrome.

Review: Terlipressin for hepatorenal syndrome

Comparison: 1 Terlipressin alone or with albumin versus no intervention or albumin

Outcome: 5 Mortality in trials on type 1 hepatorenal syndrome

Study or subgroup	Treatment n/N	Control n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
Sanyal 2008	32/56	35/56		43.0 %	0.91 [0.67, 1.24]
Solanki 2003	7/12	12/12		27.7 %	0.60 [0.37, 0.97]
Neri 2008	12/26	21/26		29.3 %	0.57 [0.36, 0.90]
Total (95% CI)	**94**	**94**		**100.0 %**	**0.71 [0.51, 0.98]**

Total events: 51 (Treatment), 68 (Control)

Heterogeneity: $Tau^2 = 0.04$; $Chi^2 = 3.84$, df = 2 (P = 0.15); $I^2 = 48\%$

Test for overall effect: Z = 2.08 (P = 0.038)

Test for subgroup differences: Not applicable

Analysis 1.6. Comparison 1 Terlipressin alone or with albumin versus no intervention or albumin, Outcome 6 Mortality in trials on terlipressin and albumin.

Review: Terlipressin for hepatorenal syndrome

Comparison: 1 Terlipressin alone or with albumin versus no intervention or albumin

Outcome: 6 Mortality in trials on terlipressin and albumin

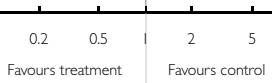
Study or subgroup	Treatment n/N	Control n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
Neri 2008	12/26	21/26		19.1 %	0.57 [0.36, 0.90]
Solanki 2003	7/12	12/12		17.8 %	0.60 [0.37, 0.97]
Sanyal 2008	32/56	35/56		31.7 %	0.91 [0.67, 1.24]
Mart n-Llah 2008	17/23	19/23		31.4 %	0.89 [0.66, 1.22]
Total (95% CI)	**117**	**117**		**100.0 %**	**0.77 [0.61, 0.97]**

Total events: 68 (Treatment), 87 (Control)

Heterogeneity: $Tau^2 = 0.02$; $Chi^2 = 4.75$, df = 3 (P = 0.19); $I^2 = 37\%$

Test for overall effect: Z = 2.18 (P = 0.029)

Test for subgroup differences: Not applicable



Analysis 1.7. Comparison 1 Terlipressin alone or with albumin versus no intervention or albumin, Outcome 7 Mortality in trials with a low risk of selection bias.

Review: Terlipressin for hepatorenal syndrome

Comparison: 1 Terlipressin alone or with albumin versus no intervention or albumin

Outcome: 7 Mortality in trials with a low risk of selection bias

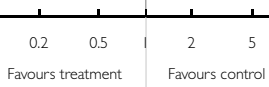
Study or subgroup	Treatment n/N	Control n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
Mart n-Llah 2008	17/23	19/23		31.4 %	0.89 [0.66, 1.22]
Neri 2008	12/26	21/26		19.1 %	0.57 [0.36, 0.90]
Solanki 2003	7/12	12/12		17.8 %	0.60 [0.37, 0.97]
Sanyal 2008	32/56	35/56		31.7 %	0.91 [0.67, 1.24]
Total (95% CI)	**117**	**117**		**100.0 %**	**0.77 [0.61, 0.97]**

Total events: 68 (Treatment), 87 (Control)

Heterogeneity: $Tau^2 = 0.02$; $Chi^2 = 4.75$, df = 3 (P = 0.19); $I^2 = 37\%$

Test for overall effect: Z = 2.18 (P = 0.029)

Test for subgroup differences: Not applicable



Analysis 1.8. Comparison 1 Terlipressin alone or with albumin versus no intervention or albumin, Outcome 8 Mortality analysed using a fixed effect model.

Review: Terlipressin for hepatorenal syndrome

Comparison: 1 Terlipressin alone or with albumin versus no intervention or albumin

Outcome: 8 Mortality analysed using a fixed effect model

Study or subgroup	Treatment n/N	Control n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Sanyal 2008	32/56	35/56		38.4 %	0.91 [0.67, 1.24]
Solanki 2003	7/12	12/12		13.7 %	0.60 [0.37, 0.97]
Mart n-Llah 2008	17/23	19/23		20.8 %	0.89 [0.66, 1.22]
Neri 2008	12/26	21/26		23.0 %	0.57 [0.36, 0.90]
Yang 2001	0/8	3/7		4.1 %	0.13 [0.01, 2.10]
Total (95% CI)	**125**	**124**		**100.0 %**	**0.76 [0.63, 0.91]**

Total events: 68 (Treatment), 90 (Control)

Heterogeneity: Chi^2 = 6.56, df = 4 (P = 0.16); I^2 =39%

Test for overall effect: Z = 2.92 (P = 0.0035)

Test for subgroup differences: Not applicable

APPENDICES

Appendix 1. Searches

Database	Dates searched	Search terms	References identified
Cochrane Hepato-Biliary Group Controlled Trials Register	January 2012	(terlipressin* OR glypressin* OR vasoconstric*) AND 'hepatorenal syndrom*'	26
MEDLINE (Ovid SP)	1946 to January 2012	1. exp Vasoconstrictor Agents/ 2. (terlipressin* or glypressin* or vasoconstric*).mp. [mp=title, original title, abstract, name of substance word, subject heading word]	44

(*Continued*)

		3. 1 or 2 4. exp Hepatorenal Syndrome/ 5. hepatorenal syndrom*.mp. [mp=title, original title, abstract, name of substance word, subject heading word] 6. 4 or 5 7. 6 and 3 8. (random* or blind* or placebo* or meta-analysis).mp. [mp=title, original title, abstract, name of substance word, subject heading word] 9. 8 and 7	
Cochrane Central Register of Controlled Trials (CENTRAL) in *The Cochrane Library*	Issue 1 of 12, 2012	#1 MeSH descriptor Vasoconstrictor Agents explode all trees 8487 #2 terlipressin* OR glypressin* OR vasoconstric* 3302 #3 (#1 OR #2) 10371 #4 MeSH descriptor Hepatorenal Syndrome explode all trees 37 #5 hepatorenal syndrom* 120 #6 (#4 OR #5) 120 #7 (#3 AND #4) 23	16
EMBASE (Ovid SP)	1974 to January 2012	1. exp Terlipressin/ 2. exp Vasoconstrictor Agent/ 3. (terlipressin* or glypressin* or vasoconstric*).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name] 4. 1 or 3 or 2 5. exp Hepatorenal Syndrome/ 6. hepatorenal syndrom*.mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name] 7. 6 or 5 8. 4 and 7 9. (random* or blind* or placebo* or meta-analysis).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name] 10. 8 and 9	160

(*Continued*)

Science Citation Index Expanded (http://apps.isiknowledge.com)	1900 to January 2012	# 5 96 #4 AND #3 # 4 999,592 TS=(random* or blind* or placebo* or meta-analysis) # 3 350 #1 AND #2 # 2 1,675 TS=(hepatorenal syndrom*) # 1 34,324 TS=(terlipressin* or glypressin* or vasoconstric*)	96

WHAT'S NEW

Last assessed as up-to-date: 31 January 2012.

Date	Event	Description
9 April 2012	Amended	Based on peer review comments, exclusion of all other intervention comparisons than terlipressin alone or with albumin versus no intervention, placebo or albumin
9 March 2012	Amended	Based on peer review comments, the outcomes are changed with inclusion of quality of life according to the Cochrane Hepato-Biliary Group recommendations
11 January 2012	New search has been performed	New searches are performed, and additional trials were identified and included in the review
9 March 2011	Amended	Based on peer review comments, we changed the definitions of primary outcomes. In the present version, all outcomes are defined as primary based on recommendations from peer review comments
11 January 2011	New citation required but conclusions have not changed	Additional trials are included (the original review included data from three trials and the updated review has data from eight trials). The overall conclusions are not changed

CONTRIBUTIONS OF AUTHORS

LG drafted the original and updated review. Three authors LG, KC and AK have participated in the literature searches and data extraction. All authors have participated in revision of the review.

DECLARATIONS OF INTEREST

None of the authors have financial, academic, or personal conflicts of interests with regard to the submitted work.

SOURCES OF SUPPORT

Internal sources

- No internal funding received, Not specified.

External sources

- No external funding received, Not specified.

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

- The previous version of the present review included three trials (Hadengue 1998; Yang 2001; Solanki 2003). Based on the changes in the outcome measures assessed, we were unable to extract data from one of these trials (Hadengue 1998). We were therefore unable to include the trial in our analyses. The updated review includes six trials, but only includes data from five trials. Inclusion of the new trials confirmed the findings of the previous review.

- We have updated the criteria for assessment of the outcome measure on hepatorenal syndrome based on the latest criteria (described by the International Ascites Club (www.icascites.org/)). Based on these criteria, we have excluded urine output and creatinine clearance from our analyses.

- The assessment of bias control is revised, and the statistical analyses revised the included incorporation of trial sequential analysis.

- Following review comments and the guidelines specified by the Cochrane Hepato-biliary Group, we added quality of life as an outcome measure and classed all of our outcome measures as primary outcomes.

- We originally planned to include trials comparing different vasoactive drugs, but excluded these analyses based on review comments.

INDEX TERMS

Medical Subject Headings (MeSH)

Albumins [therapeutic use]; Hepatorenal Syndrome [classification; *drug therapy]; Lypressin [*analogs & derivatives; therapeutic use]; Randomized Controlled Trials as Topic; Vasoconstrictor Agents [*therapeutic use]

MeSH check words

Humans