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Terlipressin in hepatorenal syndrome: a systematic review and meta-analysis

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Abstract

Background—Hepatorenal syndrome (HRS) is a common complication in patients with cirrhosis or fulminant liver failure. We systematically reviewed the benefits and harms of using terlipressin, a novel vasoconstricting agent in patients with HRS.

Methods—We searched MEDLINE, SCOPUS, and conference proceedings for relevant trials of terlipressin. Results were summarized using the random-effects model.

Results—Eight trials (320 participants) were included. When compared with placebo, terlipressin-treated patients had higher HRS reversal (odds ratio [OR] 7.47, 95% confidence interval [CI] 3.17–17.59), mean arterial pressure (weighted mean difference [WMD] 11.26 mmHg, 95% CI 1.52–21), and urine output. There was a significant increase in ischemic adverse events with terlipressin when compared to placebo. There was mild-to-moderate heterogeneity in these analyses. There was no significant difference between terlipressin and noradrenaline in HRS reversal (OR 1.23, 95% CI, 0.43–3.54), mean arterial pressure, and urine output. Side-effect profile did not differ between terlipressin and noradrenaline.

Conclusion—Terlipressin improves HRS reversal and other surrogate outcome measures compared with placebo, but no significant differences for these outcomes were noted when comparing terlipressin and noradrenaline. Terlipressin is a potential therapeutic option for HRS, but larger trials comparing terlipressin to other widely used vasoconstrictors are warranted.

Keywords

Terlipressin; Hepatorenal syndrome; Vasoconstrictors

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Background

Hepatorenal syndrome (HRS) is a common complication of patients with cirrhosis or fulminant liver failure, due to functional renal impairment without an identifiable cause [1–3]. Approximately 39% of patients with cirrhosis and ascites will develop hepatorenal syndrome within 5 years of the disease Results of this systematic review were presented as a poster at the American Society of Nephrology annual meeting in October 2009, San Diego, USA. onset [4]. Criteria for the diagnosis of HRS developed by the International Club of Ascites include the following: presence of cirrhosis and ascites, serum creatinine >1.5 mg/dl (or 133 micromoles/l), no improvement in serum creatinine (decrease equal to or less than 1.5 mg/dl) after at least 48 h of diuretic withdrawal and volume expansion with albumin, absence of shock, no current or recent treatment with nephrotoxic drugs, absence of parenchymal kidney disease as indicated by proteinuria >500 mg/day, microhematuria (>50 red blood cells/high power field, and/or abnormal renal ultrasound scanning. Type 1 HRS was defined as a rapidly progressive reduction in renal function, e.g., a doubling of serum creatinine to greater than 2.5 mg/dl in less than 2 weeks and failure of renal function to improve following diuretic withdrawal and plasma volume expansion; type 2 HRS was defined as serum creatinine greater than 1.5 mg/dl or 133 μmol/l, which follows a steady or slowly progressive course [5]. HRS portends extremely poor outcome [4].

Liver transplantation offers the potential for complete renal and hepatic recovery in eligible patients with cirrhosis complicated by HRS. It is imperative, however, to prevent or reverse type 1 HRS and improve survival among patients who are waiting or being evaluated for liver transplantation. Moreover, patients with pre-transplant renal impairment have higher mortality and longer wait time compared with matched liver transplant candidates without HRS for any given model for end-stage liver disease (MELD score) and have a poor outcome post liver transplantation [6–9].

HRS pathogenesis involves the interplay between the activation of vasoconstrictor systems and the reduction in the activity of vasodilator systems. The arterial vasodilatation in the splanchnic circulation plays a central role in the renal function deterioration and the hemodynamic changes and is mediated by an increased production and/or activity of local vasodilators, with nitric oxide being the most important. As the liver disease progresses in severity, a critical level of hypoperfusion is achieved, with subsequent activation of renin-angiotensin and sympathetic nervous systems. Renal vasodilatory systems are not able to offset the maximal effect of endogenous vasoconstrictors, leading to an uncontrolled renal vasoconstriction [2, 4, 5].

Peripheral arterial vasodilation theory for HRS, proposed in 1988, has resulted in several pharmacologic interventions that function as systemic vasoconstrictors [10, 11]. Promising but limited studies have been reported using α-adrenergic agonists (midodrine and noradrenaline), vasopressin analogs (ornipressin and terlipressin), and somatostatin analog (octreotide) [12, 13]. Octreotide, in combination with midodrine and albumin infusion improved renal and systemic hemodynamics by the systemic vasoconstrictor effect of midodrine and the inhibition of endogenous vasodilator release action of octreotide [14].

Terlipressin, an analog of the natural hormone arginine-vasopressin, used alone or in combination with albumin, has been studied in clinical trials for the reversal of HRS [15–19]. Our main objective was to systematically review the evidence of terlipressin's effect on renal function compared to placebo or to other vasoconstricting agents in patients with HRS. We also aimed to assess terlipressin's effects on short- and long-term survival and its adverse effects.

Methods

Data sources and search strategy

We searched MEDLINE (1966-January 2009), SCO-PUS (January 2009), and abstracts presented from 2004 to 2008 at the annual meetings of the American Society of Nephrology, National Kidney Foundation, European Renal Association, Digestive Disease Week, and the United European Gastroenterology Federation using the following medical subject heading terms: hepatorenal syndrome, terlipressin, and vasoconstrictor agents. References of the included studies were also searched for additional studies. There were no language restrictions. Two reviewers (MD and SDN) independently and in duplicate screened all abstracts that indicated that each study was a randomized controlled trial (RCT) evaluating terlipressin alone or in combination with intravenous albumin in the treatment of HRS. After obtaining the candidate trials, the same reviewers independently and in duplicate assessed eligibility from the full-text articles.

Inclusion criteria and outcome measures

Eligible studies had the following characteristics: (a) they were RCTs of any duration of terlipressin used alone or in combination with intravenous albumin for the treatment of HRS type 1 or type 2, as defined by the International Ascites Club criteria [5], (b) the intervention was the use of terlipressin versus placebo or another vasoconstrictor, with or without the addition of albumin, as long as the only difference between the two arms was the use of terlipressin, and (c) trial participants were adult subjects (≥18 years of age). Cross-over trials were also considered for inclusion if the study provided data for the first half of the study period.

The primary outcome measure was the resolution of HRS defined as a decrease in serum creatinine level to ≤1.5 mg/dl during treatment, without the need for dialysis. Secondary outcome measures included the following: (a) survival rates at days 30, 60, 90, and 180 where data were available, (b) change in serum creatinine (in mg/dl) at the end of the study period, (c) change in the mean arterial pressure (in mmHg) and urinary output (in ml) at the end of treatment period, and (d) major adverse events (non-fatal myocardial infarction, arrhythmias, peripheral vascular ischemia, and intestinal ischemia).

Data collection

Two reviewers (MD and SDN) extracted data after assessing and reaching consensus for eligible studies using a standardized data extraction form. The same reviewers independently assessed each trial and extracted data about the characteristics of the participants, the protocols used for the administration of terlipressin and albumin, the baseline kidney function, and the measured outcomes. Disagreements between reviewers were resolved in consultation with SD.

Study quality

The quality of included studies was assessed independently by the same reviewers without blinding to authorship or journal using the checklist developed by the Cochrane collaboration [20]. The quality items assessed were allocation concealment, intention-to-treat analysis, completeness to follow-up and blinding of investigators, participants, and outcome assessors.

Data analysis and synthesis

Dichotomous data (reversal of HRS and adverse events) results were expressed as odds ratio (OR) with 95% confidence interval (CI) and continuous variables (change in serum

creatinine and urinary output at the end of study period and change in mean arterial pressure after therapy initiation) were analyzed using the weighted mean difference (WMD) and its 95% CI if different scales had been used. All *P* values were reported as two sided. Data were pooled using the Der Simonian-Laird random-effects model [21], but the fixed-effects model was also analyzed to ensure robustness of the model chosen and susceptibility to the outliers. Analyses were performed using Revman 5 (©2007, The Cochrane Collaboration, UK).

Heterogeneity was analyzed using a chi-squared test on N-1 degrees of freedom, with an alpha of 0.05 used for statistical significance and with the I^2 test [22]. I^2 values greater than 25, 50, and 75% were considered evidence of low, moderate, and high levels of statistical heterogeneity, respectively. If substantial statistical heterogeneity was noted (I^2 >50%), we planned to explore individual study characteristics and those of subgroups of the main body of evidence. We performed sensitivity analyses to explore the influence of statistical models (fixed-and random-effects model) on effect size and the influence of each study by excluding one study at a time to assess the robustness of results. We performed separate analysis for studies that compared terlipressin to placebo and terlipressin to other vasoconstrictors.

Results

Search results

The combined search of MEDLINE, SCOPUS, and the conference proceedings identified 267 articles. We excluded 246 studies because they were non-randomized or had outcomes irrelevant to this review. The full-text assessment of the 21 potentially relevant articles resulted in the identification of 8 eligible trials involving 320 participants [15–18, 23–26]. Trials excluded at this stage were either review articles or studies that analyzed other outcomes (Fig. 1).

Trial characteristics

Terlipressin (with or without albumin) vs. placebo (with or without albumin)— Three of the six studies compared terlipressin plus albumin to albumin alone [17, 22, 26]. Two studies compared terlipressin plus albumin to albumin plus placebo [16, 23], and a cross-over study compared terlipressin to placebo [25]. The number of participants in these studies ranged from 15 to 112. Most studies enrolled adult cirrhotic patients with type 1 HRS, while two enrolled both type 1 and 2 HRS. The treatment regimens varied among studies. Terlipressin was administered intravenously as 0.5–2 mg every 6 h in two studies [16, 24], 1–2 mg every 4 h in one study [17], and 1 mg every 12 h in three studies [18, 25, 26]. The albumin dose varied between 20 and 40 mg per day, with one study using a loading dose of 100 mg in the first day, followed by 25 mg per day in the subsequent days [16]. Except for two studies [25, 26], terlipressin therapy was continued for 15 days or until the reversal of HRS. Other characteristics of participants and interventions of the included trials are listed in Table 1.

Terlipressin versus noradrenaline—Two studies compared terlipressin plus albumin with noradrenaline plus albumin [15, 18]. Noradrenaline was administered at the rate of 0.1–0.7 μg/kg/min in the study by Alessandria et al. [18], while Sharma et al. [15] used 0.5–3 mg/h continuous infusion of noradrenaline. Terlipressin was administered intravenously as 0.5–2 mg every 6 h in one study [15] and as 1–2 mg every 4 h in the other one [18] (Table 1).

Trial quality

By current methodological standards, trial quality was variable. Allocation concealment was unclear in all trials. Participants, investigators, and outcome assessors were not blinded in any of the trials. Only one of the 8 trials was reported to be analyzed on an intention-to-treat basis. The drop-out rate ranged from 0 to 15% and did not differ between the treatment and control groups.

Study outcomes

Terlipressin (with or without albumin) vs. placebo (with or without albumin)

Reversal of HRS: There was a significant increase in the reversal of HRS with terlipressin with or without albumin in comparison with placebo (4 trials, 234 patients, $n = 55/117$ vs. 14/117, OR 7.47, 95% CI 3.17–17.59, $P < 0.00001$) [16, 17, 23, 24]. There was mild heterogeneity (insignificant) noted among the included trials (heterogeneity $chi^2 = 3.96$, $I^2 = 24\%$, $P = 0.27$; Fig. 2).

Mean arterial pressure: There was a significant difference in mean arterial pressure with terlipressin in comparison with placebo after therapy initiation (Fig. 3).

Urine output: There was a significant difference in the urine output with terlipressin in comparison with placebo at the end of treatment period (Fig. 4).

Serum creatinine: There was a significant difference in the serum creatinine with terlipressin in comparison with placebo at the end of treatment period (2 trials, 76 patients, WMD −1.77 mg/dl, 95% CI −3.57 to 0.04, $P = 0.05$) with significant heterogeneity noted between the included trials ($chi^2 = 46.05$, $I^2 = 96\%$, $P < 0.00001$) [23, 24].

Survival rates: Sufficient data were not available to conduct a meta-analysis for this outcome. However, we tabulated the effects of terlipressin on survival at 15, 30, 90, and 180 days, which were reported in the studies, when compared with the control groups (Table 2).

Plasma renin activity and serum aldosterone: Both plasma renin activity and plasma aldosterone level decreased after terlipressin treatment. However, these variables were reported in only 2 trials, therefore not enough data were available to perform a meta-analysis [18, 25]. In patients who responded to terlipressin therapy, a significant decrease occurred in plasma aldosterone and plasma renin activity at the end of the study period (778 ± 262 vs. 447 ± 138 ng/dl, and 21 ± 5 vs. 7 ± 3 ng/ml/h in the study by Alessandria et al. [18] and 1,227 ± 378 vs. 1,098 ± 413 and 202 ± 70 vs. 112 ± 38 pg/ml, respectively, in the study by Hadengue et al. [25]).

Adverse events: In six studies, 7 ischemic events were reported in terlipressin-treated patients, while none of the placebo-treated patients experienced ischemic events.

Terlipressin versus noradrenaline

Reversal of HRS: No significant difference in reversal of HRS was noted at the end of the study period (2 trials, 62 patients, 20/32 vs. 17/30, OR 1.23, 95% CI 0.43–3.54, $P = 0.70$) between terlipressin and nor-adrenaline with no heterogeneity between the included trials (heterogeneity $chi^2 = 0.39$, $I^2 = 0\%$, $P = 0.53$; Fig. 2) [15, 18].

Mean arterial pressure: There was no significant difference in the mean arterial pressure after therapy initiation between terlipressin and noradrenaline (Fig. 3) [15, 18].

Urine output: There was no significant difference in urine output at the end of study period between terlipressin and noradrenaline (Fig. 4) [15, 18].

Serum creatinine: There was no difference in the serum creatinine at the end of the study period between terlipressin and noradrenaline (2 trials, 62 patients, WMD 0.20 mg/dl, 95% CI −0.08, 0.47, $P = 0.17$) with no heterogeneity between the included trials (heterogeneity $chi^2 = 0.39$, $I^2 = 0\%$, $P = 0.53$) [15, 18].

Survival rates: In the study by Alessandria et al. [18], 11/12 patients were alive in the terlipressin arm, while 8/10 patients were alive in the noradrenaline arm at 30-day follow-up. Similarly, in the study by Sharma et al. [15], 11/20 patients were alive in both noradrenaline and terlipressin groups at the end of 2 weeks (Table 2).

Adverse events: Sharma et al. [15] reported that four patients had abdominal cramps and one patient had ST segment depression >0.1 mV in the terlipressin arm, while two patients had ventricular ectopies in the noradrenaline group. Alessandria et al. [18] reported no major adverse events with terlipressin or noradrenaline.

Sensitivity analysis

There was minimal heterogeneity (but statistically insignificant) noted in the analysis of the primary outcome. The fixed-effects analysis of the risk of HRS reversal yielded effect sizes that were similar in magnitude, direction, and significance to those obtained from random-effects analysis (OR). The sensitivity analysis on the risk of HRS reversal with terlipressin after the exclusion of each individual study, one at a time yielded effect sizes similar in magnitude and direction to the overall estimates.

Discussion

Our review suggests that the use of terlipressin improved mean arterial pressure that results in higher urine output and reversal of HRS when compared to placebo. But no such differences were found when terlipressin was compared with noradrenaline. There was a higher incidence of major adverse events with terlipressin when compared to placebo, while the side-effect profile did not differ between terlipressin and noradrenaline. Limited data suggest that terlipressin might improve survival rates in comparison with placebo but no additional effects were seen when compared to noradrenaline.

With the higher mortality rates noted in patients with HRS, several agents have been explored as bridging therapy to liver transplantation. Most treatment options targeted splanchnic vasoconstriction along with volume expansion with albumin. Vasoconstrictors used for HRS include vasopressin analogs (ornipressin and terlipressin), somatostatin analogs (octreotide), and alpha-adrenergic agonists (midodrine). Data supporting the use of midodrine and octreotide were mostly observational in nature and have not been compared directly to treatment with terlipressin or noradrenaline [13, 14]. Even though earlier reports showed optimistic results with ornipressin and vasopressin, the ischemic side effects limited their use in HRS. Earlier uncontrolled studies reported a larger HRS reversal and fewer ischemic side effects with terlipressin that prompted proof of concept studies.

The effect size of individual terlipressin studies decreased as the sample size increased, suggesting the exaggerated benefits seen in earlier studies with smaller sample size. The study by Sanyal et al. [16] had the largest number of patients and reported only a three-fold higher HRS reversal. Of note, about 50% of patients included in these studies did not respond to terlipressin. The lack of benefit seen in these patients might be related to the

severity of liver failure (the higher the MELD score, the lower the response) or due to the reduction in cardiac output seen with vasoconstrictors.

Individual studies reported higher survival rates with terlipressin in comparison with placebo, but these could not be pooled because they reported mortality rates inconsistently at different time periods (15-, 30-day survival rate, etc.). Further, none of these studies was designed to assess the effects of terlipressin on mortality rates. Previous meta-analyses on this topic concluded that terlipressin has higher efficacy than placebo in reversal of HRS [27–29]. These analyses included fewer trials than our analysis; trials comparing terlipressin to noradrenaline were not included, and formal quality assessments of the included trials were not performed in some of these analyses.

Our review has a number of strengths and limitations. Strengths include a systematic search of medical databases, data extraction and analysis, and trial quality assessment by two independent reviewers based on a pre-specified protocol. Limitations of our meta-analysis include the paucity of quality data, and the included trials were of short duration and were not adequately powered to measure patient-centered outcomes such as need for dialysis and death. We could not ascertain whether the differences in the dosage of terlipressin and protocol used had any impact on the results due to the smaller number of studies identified. Most studies included in our review analyzed the efficacy of terlipressin in patients with type 1 HRS, and it may be inappropriate to extrapolate these results to patients with type 2 HRS.

Terlipressin is a potential therapeutic option for HRS but adequately powered trials that measure patient-oriented outcomes in participants with both type 1 and type 2 HRS are needed. These studies should compare the effects of terlipressin to placebo and to other widely used vasoconstrictors such as noradrenaline as the latter could be a less expensive alternative to terlipressin.

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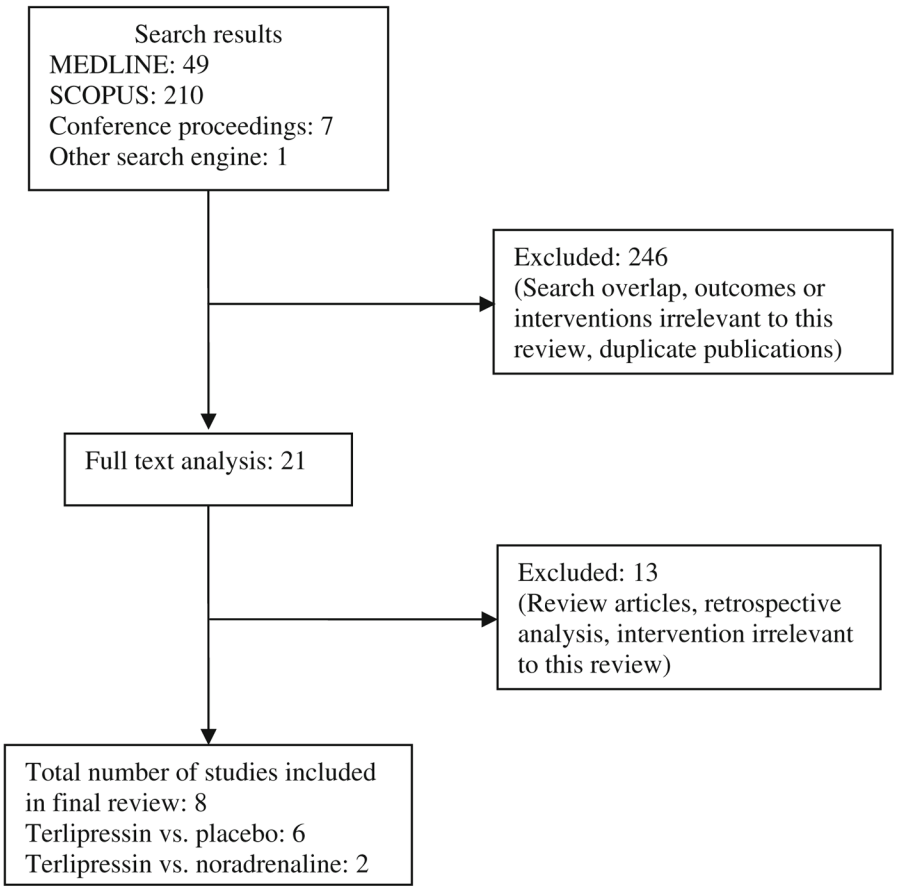

Fig. 1.
Flow chart shows number of citations retrieved by individual searches and number of trials included in review

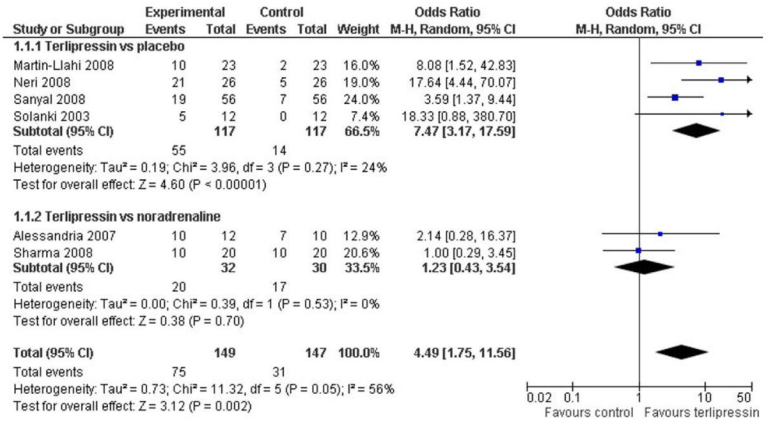

Fig. 2.
Reversal of HRS

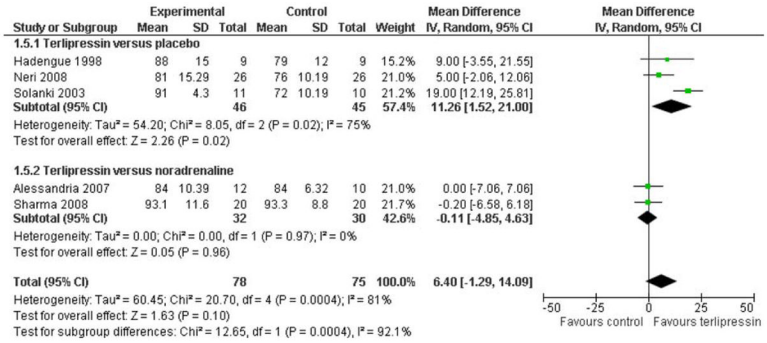

Fig. 3.
Mean arterial pressure after therapy initiation

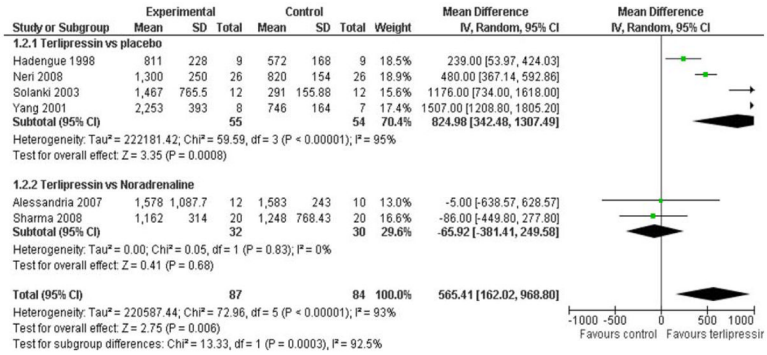

Fig. 4.
Urine output at the end of treatment period

Table 1

Characteristics of the population and interventions in the included trials of terlipressin

Study	Country	Inclusion criteria/baseline creatinine	Intervention	No. of patients (intervention/ control)	Definition of reversal of HRS	Study end-points
Terlipressin versus placebo						
Hadengue et al. [25]	France	HRS type 1	Terlipressin vs. placebo	9	N/A	Creatinine clearance, urinary output, and urinary sodium concentrations
Martin-Llahi et al. [17]	Spain	HRS type 1 or type 2 with SCr >175 μmol/l	Terlipressin + albumin vs. albumin alone	23/23	Complete response: decrease in SCr <133 μmol/l during treatment. Partial response: decrease in SCr >50% compared to baseline, but with end-of-treatment value >133 μmol/l	Primary: survival at 3 months and improvement in renal function (either complete or partial response)
Neri et al. [24]	Italy	HRS type 1	Terlipressin + albumin vs. albumin alone	26/26	Complete response: decrease in SCr to 132 μmol/l (1.5 mg/dl) or less during treatment. Partial response: decrease in 50% or greater of SCr compared with baseline to a final value higher than 132 μmol/l (1.5 mg/dl)	Improvement in renal function and survival after treatment up to 6 months
Sanyal et al. [16]	USA	HRS type 1	Terlipressin + albumin vs. placebo + albumin	56/56	Decrease in SCr to ≤1.5 mg/dl on two occasions, at least 48 h apart without HD, death or recurrence of HRS type 1 on or prior to day 14	Primary: HRS reversal at day 14. Secondary: change in SCr, treatment failure at day 14, combined treatment success and partial response, transplant-free survival at day 60, overall survival at day 60, overall and transplant-free survival at day 180
Solanki et al. [23]	India	HRS type 1	Terlipressin + albumin + FFP vs. placebo + albumin + FFP	12/12	NA	Reversal of HRS and survival at day 15
Yang et al. [26]	China	HRS type 1 or type 2	Terlipressin + albumin vs. albumin	8/7	NA	Survival at 5 and 10 days
Terlipressin versus noradrenaline						
Alessandria et al. [18]	Italy	HRS type 1 or type 2	Terlipressin + albumin vs. noradrenaline + albumin	12/10	Complete response: decrease in 30% or greater of SCr compared to baseline to a final value of 1.5 mg/dl (133 μmol/l) or lower during treatment. Partial response: decrease in 30% or greater of SCr compared to baseline to a final value higher than 1.5 mg/dl (133 μmol/l)	Complete HRS reversal

Study	Country	Inclusion criteria/baseline creatinine	Intervention	No. of patients (intervention/ control)	Definition of reversal of HRS	Study end-points
Sharma et al. [15]	India	HRS type 1 with SCr >2.5 mg/dl or CrCl <20 ml/min	Terlipressin + albumin vs. noradrenaline + albumin	20/20	Complete response: decrease in SCr to ≤1.5 mg/dl during the treatment Partial response: decrease in 50% or greater of SCr compared with baseline to a final value higher than 1.5 mg/dl	Primary: complete HRS reversal. Secondary: survival at the end of 15 days of treatment

CrCl creatinine clearance, *FFP* fresh frozen plasma, *HD* hemodialysis, *HRS* hepatorenal syndrome, *no*. number, *SCr* serum creatinine, *vs* versus

Table 2

Survival data (number of patients who survived) in the included trials of hepatorenal syndrome

Study	15 Days		30 Days		90 Days		180 Days	
	Terlipressin	Control	Terlipressin	Control	Terlipressin	Control	Terlipressin	Control
Terlipressin versus placebo [a]								
Martin-Llahi et al. [17]					6 (26%)	4 (17%)		
Neri et al. [24]	23 (87%)	14 (53%)	19 (72%)	11 (42%)	14 (54%)	5 (19%)	11 (42%)	4 (16%)
Sanyal et al. [16][b]							24 (42.9%)	21 (37.5%)
Solanki et al. [23]	5 (41.6%)	0 (0.0%)						
Terlipressin versus noradrenaline								
Alessandria et al. [18][c]			11 (91.6%)	8 (80%)	8 (66.6%)	7 (70%)	8 (66.6%)	7 (70%)
Sharma et al. [15]	11 (55%)	11 (55%)						

[a] Two studies (Yang et al. [26] and Hadengue et al. [25]) did not report mortality outcomes

[b] For patients who did not undergo liver transplantation, 7 patients (13%) in the terlipressin group and 5 patients (9%) in the placebo group survived to day 180

[c] For patients who did not undergo liver transplantation, 8 patients (66.6%) in the terlipressin group and 1 patient (10%) in the noradrenalin group were alive at 1 month. No patient who did not undergo liver transplant was alive at 6 months