Systematic Review of Randomized Trials on Vasoconstrictor Drugs for Hepatorenal Syndrome

Lise L. Gluud,[1,2] Kurt Christensen,[2] Erik Christensen,[2,3] and Aleksander Krag[1,4]

Vasoconstrictor drugs may improve renal function in hepatorenal syndrome (HRS), but the effect on mortality has not been established. We therefore performed a systematic review of randomized trials on vasoconstrictor drugs for type 1 or type 2 HRS. Mortality was the primary outcome measure. Eligible trials were identified through electronic and manual searches. Intention-to-treat random effects meta-analyses were performed. Ten randomized trials on terlipressin alone or with albumin, octreotide plus albumin, and noradrenalin plus albumin were included. The total number of patients was 376. Overall, vasoconstrictor drugs used alone or with albumin reduced mortality compared with no intervention or albumin (relative risk [RR], 0.82; 95% confidence interval [CI], 0.70-0.96). In subgroup analyses, the effect on mortality was seen at 15 days (RR, 0.60; 95% CI, 0.37-0.97) but not at 30 days (RR, 0.74; 95% CI, 0.40-1.39), 90 days (RR, 0.89; 95% CI, 0.66-1.22), or 180 days (RR, 0.83; 95% CI, 0.65-1.05). Subgroup analyses stratified by the treatments assessed showed that terlipressin plus albumin reduced mortality compared with albumin (RR, 0.81; 95% CI, 0.68-0.97). The effect was seen in subgroup analyses of type 1 but not type 2 HRS. The remaining trials were small and found no beneficial or harmful effects of the treatments assessed. *Conclusion:* Terlipressin plus albumin may prolong short-term survival in type 1 HRS. The duration of the response should be considered when making treatment decisions and in the timing of potential liver transplantations. Considering the small number of patients included, the evidence does not allow for treatment recommendations regarding type 2 HRS or any of the remaining treatment comparisons assessed. (HEPATOLOGY 2010;51: 576-584.)

Hepatorenal syndrome (HRS) is a functional renal failure associated with advanced cirrhosis.[1-3] 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.[1] Without treatment, HRS type 1 has a median survival of about 2 weeks, whereas type 2 has a median survival of about 6 months.[4]

The development of HRS is associated with the circulatory changes seen in cirrhosis with portal hypertension, including splanchnic vasodilation. This vasodilation may result in effective arterial underfilling with subsequent constriction of the renal arteries.[5-7] Increasing the splanchnic arterial tone with vasoconstrictor drugs may therefore reverse HRS. Uncontrolled studies have suggested that vasopressin improves the renal function of patients with cirrhosis.[8] However, vasopressin was abandoned due to severe ischemic complications. Subsequent studies found that the vasopressin analogues terlipressin and ornipressin were safer and had the same beneficial effects.[9-12] Similar results were found for the vasoconstrictor drugs octreotide and noradrenalin.[13,14] A systematic review with a meta-analysis of randomized trials revealed that terlipressin may reduce mortality in HRS.[15] However, the included trials had methodological problems including unclear bias control, the use of a crossover design, and short treatment durations. Furthermore, the total number of patients was 51. Subsequent trials were larger, but the results regarding clinical outcome measures—in-

Abbreviations: CI, confidence interval; HRS, hepatorenal syndrome; RR, relative risk.

From the [1]Department of Internal Medicine, Copenhagen University Hospital Gentofte, Hellerup, Denmark; the [2]Cochrane Hepato-Biliary Group, Copenhagen Trial Unit, Centre for Clinical Intervention Research, Copenhagen, Denmark; the [3]Clinic of Internal Medicine, Bispebjerg University Hospital, Copenhagen, Denmark; and the [4]Department of Medical Gastroenterology, Hvidovre University Hospital, Hvidovre, Denmark.

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Address reprint requests to: Lise Lotte Gluud, M.D., D.Sc., Department of Internal Medicine, Copenhagen University Hospital Gentofte, Niels Andersensvej 65, 2900 Hellerup, Denmark. E-mail: liselottegluud@yahoo.dk; fax: (45)-3545-7101.

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cluding mortality—remained inconclusive.[16-19] A recent meta-analysis including five trials revealed a beneficial effect of terlipressin alone or with albumin compared with placebo alone or with albumin on reversal of HRS.[20] No effect on survival was identified. The included trials were single-blind or double-blind using a parallel arm or crossover design. The decision to exclude trials without blinding (but include single-blind trials) while including trials with unclear randomization is debatable.[21,22] Unlike randomization, the evidence concerning the importance of blinding to the control of bias is inconsistent.[21,22] No association between single-blinding and the control of bias has been identified. Furthermore, it may be argued that including data from both periods of crossover trials when assessing a disease with a fluctuating course is debatable. Accordingly, we performed a systematic review with meta-analyses of randomized trials on vasoconstrictor drugs for HRS.

Materials and Methods

Data Sources and Study Selection. The present systematic review is based on a published protocol.[15] The review includes randomized trials on patients with type 1 or 2 HRS[1,3] without restrictions regarding the control of bias, publication status, or language. The treatment comparisons included (1) vasoconstrictor drugs alone or with albumin versus no intervention or albumin and (2) comparisons of different vasoconstrictor drugs or modes of administration. The primary outcome measure was all-cause mortality. Secondary outcome measures included reversal of HRS defined as serum creatinine <1.5 mg/dL (133 μmol/L), improvement in renal function (as defined by authors of included trials), serum creatinine, and adverse events.

Electronic searches were performed in the Cochrane Library, the Cochrane Hepato-Biliary Group Controlled Trials Register, MEDLINE, and EMBASE.[15] Manual searches included scanning of reference lists, conference proceedings, registers of ongoing trials (www.controlled-trials.com/mrct), and correspondence with experts. The last search update was performed in June 2009. Three authors (L. G., K. C., and A. K.) independently extracted data. Authors of included trials were contacted for additional information not described in the published reports. The extracted data included the proportion of patients with type 1 HRS, treatment regimens, duration of treatment, duration of follow-up, number of clinical sites, and country of origin.

Methodological Quality Assessment. The methodological quality was defined as the control of bias in the treatment comparison. The assessment was based on published reports and information provided by the authors of included trials. Based on previous evidence, the randomization methods were classified as the primary measure of bias control.[21,22] The randomization methods were evaluated by the allocation sequence generation (classified as adequate if based on a table of random numbers, computer-generated random numbers, or similar) and allocation concealment (classified as adequate if based on central randomization, identically appearing coded drug containers, serially numbered opaque sealed envelopes, or similar). We also extracted blinding (whether the trial was described as double-blind or single-blind, the method of blinding; whether patients, investigators, outcome assessors or other persons involved in the trial were blinded; and whether the adequacy of blinding was assessed),[23] the risk of attrition bias (numbers and reasons for dropouts and withdrawals and whether all patients were accounted for in the report and analysis of the trial), whether the primary outcome measure was defined and reported, whether a crossover design was used, whether sample size calculations were performed, and whether the preset sample size was achieved. For trials terminated prematurely, we registered whether this was based on predefined criteria.

Statistical Analysis. The analyses were performed using RevMan version 5.0.5 (Nordic Cochrane Centre, Copenhagen, Denmark). Meta-analyses were performed using random effects models due to expected clinical heterogeneity. Results are presented as the relative risk (RR) for binary and weighted mean differences for continuous outcomes, both with 95% confidence intervals (CIs). I^2 values were calculated as measures of the degree of inter-trial heterogeneity. Data on all patients randomized were extracted to allow intention-to-treat analyses. For patients with missing data, carry-forward of the last observed response was used. Only data from the first period of crossover trials were included. For the primary outcome measure, we performed subgroup analyses of trials stratified by the treatment regimen, the type of HRS, and methodological quality. Based on differences in the duration of follow-up in individual trials, we performed a post hoc analysis to evaluate the relationship between the treatment effect on mortality and the duration of follow-up. Based on discrepancies between the number of patients who survived and the number of patients with reversal of HRS, we performed a post hoc analysis that combined these two outcome measures. We originally planned to perform regression analyses to detect the risk of bias, including publication bias.[24] However, we did not perform these analyses, because the power to detect bias was insufficient due to the small number of trials included.

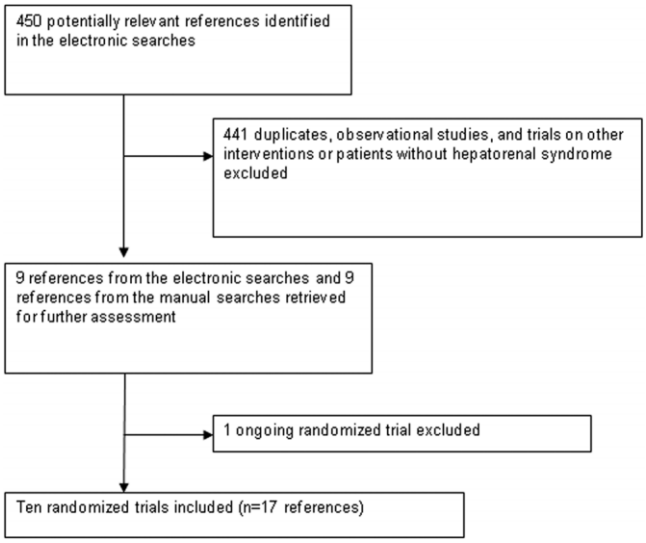

Fig. 1. Trial flow chart.

Results

In total, 450 potentially eligible references were identified through the electronic searches (Fig. 1). After reading the titles and abstracts, nine references referring to potentially eligible randomized trials were retrieved. Nine additional randomized trials were identified through the manual searches. One referred to an ongoing unpublished trial on terlipressin and albumin versus octreotide plus midodrine and albumin (www.clinicaltrials.gov, NCT00742339). This trial was excluded (no available data). The remaining 17 references referred to 10 randomized trials, which were included.[16-19,25-30] One of the included trials was published in abstract form.[29] Remaining trials were published as full paper articles. One trial was translated from Chinese.[26] The trials were conducted in the United States, Italy, Spain, Canada, France, India, China, Germany, and Russia. All trials were performed in specialized units in an intensive or semi-intensive setting.

Included Patients

The total number of patients in all trials was 376 (Table 1). HRS was diagnosed based on the criteria described by the International Club of Ascites, including evidence of cirrhosis, elevated serum creatinine after diuretic withdrawal and volume expansion plus absence of shock, ongoing infections, parenchymal renal disease, and treatment with nephrotoxic drugs.[1] In one trial, the definition of type 2 HRS included elevated serum creatinine >175 μmol/L (1.97 mg/dL) and absence of bacterial infection associated with findings of a systemic inflammatory response.[17] In the remaining trials, the type of HRS was classified based on disease progression (type 1 within 2 weeks and type 2 over more than 2 weeks). One trial[26] did not report the proportion of patients with type 1 HRS (Table 1). In six trials, all patients had type 1 HRS. In the remaining three trials, 31% to 56% of included patients had type 1 HRS.

Treatment Comparisons Assessed

The treatment comparisons included (1) terlipressin (alone or with albumin) versus no intervention, albumin or noradrenalin plus albumin, (2) octreotide plus albumin versus albumin, and (3) terlipressin plus albumin administered as continuous or bolus infusion (Table 2). The median initial dose of terlipressin was 1 mg four times daily. In six trials, the dose was increased after 3 days in nonresponders (Table 2). The dose of octreotide was 50 μg/hour. The dose of noradrenalin was adjusted to achieve an increase in the mean arterial pressure by about 10 mm Hg. The maintenance dose of albumin ranged from 20 to 60 g/day. All trials included only two allocation groups. However, in one of the largest trials on terlipressin, albumin was only recommended.[19] Accordingly, albumin was administered to 88% of patients in the treatment and control group. We were unable to retrieve separate data on patients who did not receive albumin.

Methodological Quality of Included Trials

Three trials reported both adequate allocation sequence generation and allocation concealment (Table 1).[17-19] Three trials reported either adequate allocation sequence generation or allocation concealment.[16,25,30] The remaining trials did not report randomization methods. Three trials reported double-blinding of patients and investigators by use of a placebo infusion.[19,25,27] One trial was described as single-blind without specification of whether blinding referred to patients or investigators.[16] The effect of blinding was not tested. Two trials used a two-crossover design.[25,27] One of these trials did not report mortality during the first treatment period.[25] Three

Table 1. Characteristics of Randomized Trials on Vasoconstrictor Drugs for HRS

Trial	Sample Size Treatment/Control Group	Proportion with Type 1 HRS	Adequate Randomization*
Hadengue et al.[25]	4/5	100%	−/+
Yang et al.[26]	8/7	Not reported	−/−
Solanki et al.[16]	12/12	100%	−/−
Martín-Lliahí et al.[17]	23/23	56%	+/+
Neri et al.[18]	26/26	100%	+/+
Sanyal et al.[19]	56/56	100%	+/+
Angeli et al.[29]	18/19	100%	−/−
Pomier-Layrargues et al.[27]	9/10	31%	−/−
Sharma et al.[30]	20/20	100%	+/−
Alessandria et al.[28]	10/12	41%	−/−

*Adequate (+) or unclear (−) allocation sequence generation/allocation concealment.

Table 2. Treatment Regimens Assessed in Randomized Controlled Trials on Vasoconstrictor Drugs for HRS

	Treatment Comparison	Daily Dose of Albumin (g)	Maximum Treatment Duration (days)
Hadengue et al.[25]	Terlipressin 1 mg twice daily versus no intervention	–	2
Yang et al.[26]	Terlipressin 1 mg twice daily versus no intervention	–	5
Solanki et al.[16]	Terlipressin 1 mg twice daily plus albumin versus albumin	20 g	15
Martín-Lliahí et al.[17]	Terlipressin 1 mg six times daily (increased to 2 mg six times daily in nonresponders*) plus albumin versus albumin	1 g/kg (first day) then 40 g†	15
Neri et al.[18]	Terlipressin 1 mg four times daily for 5 days then 0.5 mg four times daily for 14 days plus albumin versus albumin	1 g/kg (first day) then 40-80 g†	19
Sanyal et al.[19]	Terlipressin 1 mg four times daily (increased to 2 mg four times daily in nonresponders*) plus albumin versus albumin	100 g (first day) then 25 g‡	14
Angeli et al.[29]	Continuous versus bolus administration of terlipressin plus albumin; the dose of terlipressin was 2 mg/24 hours versus 0.5 mg six times daily (increased in nonresponders* to a maximum of 12 mg/day in both groups)	1 g/kg (first day) then 20-40 g†	Not reported
Pomier-Layrargues et al.[27]	Octreotide 50 μg/hour plus albumin versus albumin	50 g†	4
Sharma et al.[30]	Noradrenalin plus albumin versus terlipressin plus albumin; the dose of noradrenalin was adjusted by the mean arterial pressure to a maximum of 3 mg/hour; the dose of terlipressin was 0.5 mg four times daily (increased to 2 mg four times daily in nonresponders*)	20-40 g†	15
Alessandria et al.[28]	Noradrenalin plus albumin versus terlipressin plus albumin; the dose of noradrenalin was adjusted by the mean arterial pressure to a maximum of 0.7 μg/kg/minute; the dose of terlipressin was 1 mg six times daily (increased to 2 mg six times daily in nonresponders*)	40-60 g†	14

*The dose of terlipressin was increased after about 3 days in nonresponders defined as patients without decreasing serum creatinine.
†The maintenance dose of albumin was adjusted according to the central venous pressure.
‡Albumin was administered to 88% of patients in the treatment and control group.

trials reported dropouts and withdrawals and included all patients in intention-to-treat analyses.[17-19] The data from the trial published in abstract form suggested that there were losses to follow-up, although this was not specifically stated.[29] Remaining trials reported no losses to follow up. One trial followed patients to the end of treatment[16] and one to liver transplantation or death.[28] One trial followed patients to the end of treatment, but obtained additional follow-up data for some of the included patients.[30] Four trials followed patients for 2 to 6 months after treatment.[17-19,29] One trial reported sample size calculations and achieved the required sample size.[19] One trial was terminated prematurely due to unexpectedly low event rates.[17] One trial was planned to include 20 patients and included 22 patients, but did not report sample size calculations.[28] The trial published in abstract form includes 37 patients and is listed as ongoing online with a planned sample size of 70 patients (www.clinicaltrials.gov, NCT00742690).[29] Accordingly, the data from the abstract may be an interim analysis, although this is not specifically stated. Remaining trials did not report sample size calculations or whether trials were terminated early.

Vasoconstrictor Drugs Alone or With Albumin versus No Intervention or Albumin

Six of the seven trials on vasoconstrictor drugs alone or with albumin reported mortality.[16-19,26,27] A meta-analysis of these trials revealed that vasoconstrictor drugs alone or with albumin reduced mortality (78/134 [58%] versus 99/134 [74%]; RR, 0.82; 95% CI, 0.70-0.96; I^2, 0%) (Fig. 2). Only four trials reported the number of patients with reversal of HRS or improvement of renal function (Fig. 3).[16-19] All trials defined improved renal function as ≥50% reduction in serum creatinine and compared terlipressin alone or with albumin versus no intervention or albumin. The trials found that vasoconstrictor drugs (terlipressin alone or with albumin) increased the proportion of patients with reversal of HRS (RR, 3.76; 95% CI, 2.21-6.39) or improved renal function (RR, 2.00; 95% CI, 1.11-3.62). Four trials reported posttreatment serum creatinine in both treatment groups.[16,18,26,27] A meta-analysis of these trials revealed considerable intertrial heterogeneity (weighted mean difference, −128.29; 95% CI, −229.73 to −26.84; I^2, 97%).

Three trials[17-19] reported the number of withdrawals due to adverse events (6/105 [6%] versus 0/105 [0%]; RR, 4.81; 95% CI, 0.84-27.56; I^2, 0%). The number of adverse events were reported in four trials with 117 patients in the treatment and control group.[16-19] The trials compared terlipressin alone or with albumin versus no intervention or albumin. A meta-analysis revealed that the treatment group had an increased risk of cardiovascular adverse events, including cardiac arrhythmia, myocardial infarction, suspected intestinal or peripheral ischemia,

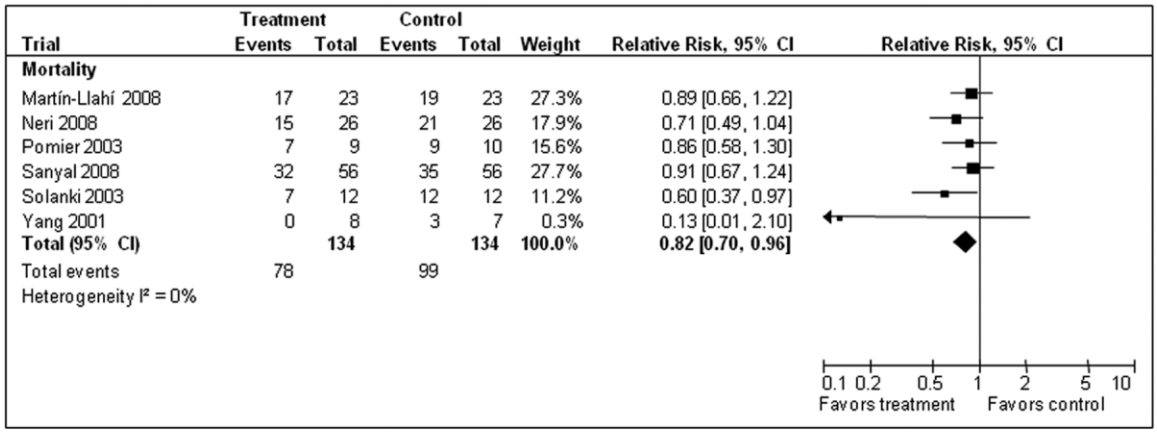

Fig. 2. Forest plot of a random effects meta-analysis of randomized trials on vasoconstrictor drugs alone or with albumin versus no intervention or albumin for HRS. The outcome measure is all-cause mortality.

and arterial hypertension (14% versus 0%; RR, 9.00; 95% CI, 2.14-37.85; I^2, 0%). Twenty-one percent of patients in the treatment group and 2% of patients in the control group experienced abdominal pain and diarrhea (RR, 6.82; 95% CI, 0.79-59.15; I^2, 0%). There were no differences between treatment and control groups regarding any of the remaining adverse events: hepatic encephalopathy (70%), bacterial infections (46%), circulatory overload (24%), gastrointestinal bleeding (9%), respiratory distress or acidosis (3%), chest pain (5%), and livedo reticularis (1%).

Subgroup Analyses

Type of Vasoconstrictor Drug. We repeated the primary meta-analysis on mortality with trials stratified by the treatments assessed (Table 3). Subgroup analyses found a beneficial effect of terlipressin alone or with albumin (RR, 0.80; 95% CI, 0.66-0.97). As previously described, one of the included trials on terlipressin, administered albumin to 88% of patients in the treatment and control group.[19] There was a beneficial effect of terlipressin plus albumin irrespective of whether this trial was included (RR, 0.81; 95% CI, 0.68-0.97) or excluded from the analysis (RR, 0.75; 95% CI, 0.61-0.93). The remaining subgroup analyses included few patients and no differences were found for any of the remaining treatment comparisons (Table 3).

Type of Hepatorenal Syndrome. Three trials only included patients with type 1 HRS.[16,18,19] A meta-analysis

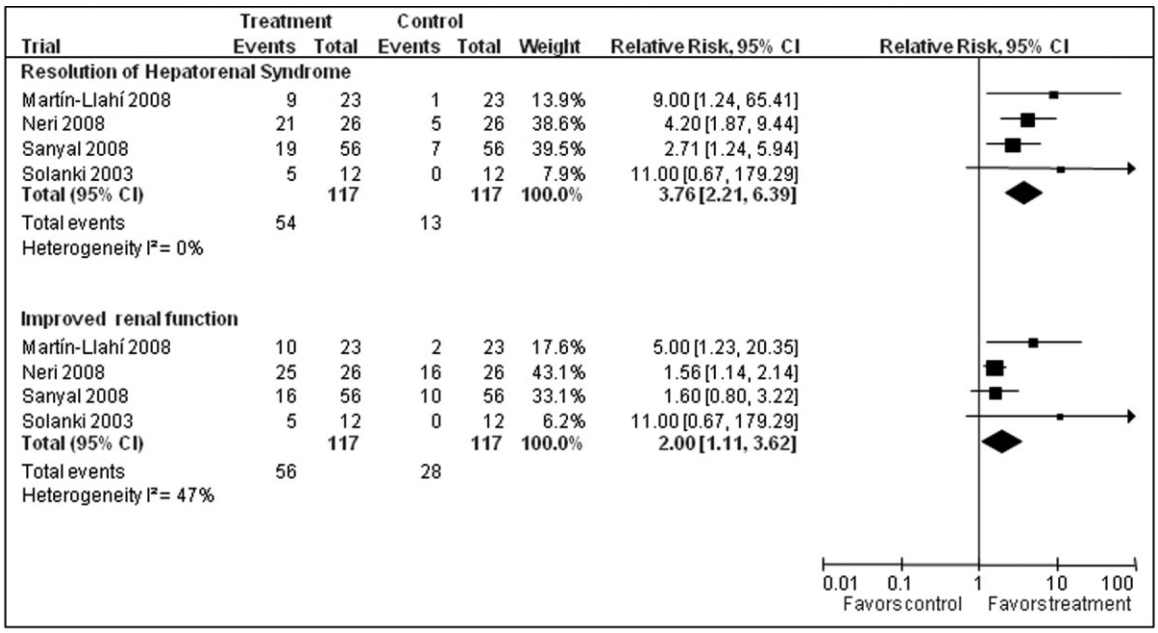

Fig. 3. Forest plots of random effects meta-analyses on terlipressin plus albumin versus albumin for patients with HRS. The outcome measures are reversal of HRS and improved renal function. The included patients received terlipressin alone or with albumin versus no intervention or albumin.

Table 3. Subgroup Meta-Analyses of Mortality in Randomized Trials on Vasoconstrictor Drugs for HRS

Treatment	Experimental Group	Control Group	Meta-analysis*
Terlipressin alone or with albumin versus no intervention or albumin	71/125 (57%)	90/124 (73%)	0.80 (0.66–0.97)
Terlipressin plus albumin versus albumin†	71/117 (61%)	87/117 (74%)	0.81 (0.68–0.97)
Terlipressin versus no intervention‡	0/8 (0%)	3/7 (43%)	0.13 (0.01–2.10)
Octreotide plus albumin versus albumin	7/9 (78%)	9/10 (90%)	0.86 (0.58–1.30)

*RR with 95% CI.

†When excluding the trial in which only 88% of patients received albumin, the RR was 0.75 (95% CI, 0.61–0.93).

‡When including the trial in which 12% of patients received terlipressin versus no intervention, the RR was 0.49 (95% CI, 0.06–3.87).

of these trials revealed that vasoconstrictor drugs plus albumin reduce mortality (54/94 [57%] versus 58/94 [62%]; RR, 0.77; 95% CI, 0.61, 0.98; I^2, 18%). Three trials included both patients with type 1 or type 2 HRS,[17,26,27] but did not report mortality data separately for these two patient groups. A meta-analysis of the trials including patients with type 1 or type 2 HRS revealed no apparent effect of vasoconstrictor drugs alone or with albumin (24/40 [60%] versus 31/40 [78%]; RR, 0.86; 95% CI, 0.65-1.15; I^2, 16%).

Methodological Quality. A meta-analysis that excluded the trial with unclear allocation sequence generation and allocation sequence revealed a beneficial effect of vasoconstrictor drugs on mortality (RR, 0.82; 95% CI, 0.70-0.97). The effect was not identified when only trials reporting both randomization methods adequately were included (RR, 0.85; 95% CI, 0.71-1.03). Likewise, no effect of vasoconstrictor drugs was seen when only trials with adequate double-blinding were included (RR, 0.90; 95% CI, 0.70-1.14).

Post Hoc Analyses. All trials on terlipressin plus albumin versus albumin reported the effect of treatment in relation to the treatment duration. When analyzing the effect of treatment on mortality in relation to the duration of follow-up, the relative risks after 15 days suggested a more beneficial effect (RR, 0.60; 95% CI, 0.37-0.97) than after 30 days (RR = 0.74; 95% CI = 0.40-1.39), 60 days (RR, 0.71; 95% CI, 0.31-1.48), 90 days (RR, 0.89; 95% CI, 0.66-1.22), or 180 days (RR, 0.83; 95% CI, 0.65-1.05).

As described above, only trials on terlipressin plus albumin versus albumin reported reversal of HRS. In these trials, 46 patients randomized to terlipressin plus albumin survived, whereas 54 had reversal of HRS. These data suggest that some patients died in spite of the improved renal function. Accordingly, a clinically relevant outcome measure would be survival with reversal of HRS. We attempted to perform a post hoc analysis combining these two outcome measures, but were only able to extract the necessary data from one trial.[19] The trial found a beneficial effect of terlipressin plus albumin on the composite outcome measure of survival plus reversal of HRS (RR, 0.76; 95% CI, 0.61-0.93).

Randomized Comparisons of Vasoconstrictor Drugs or Mode of Administration

Both trials on noradrenalin plus albumin versus terlipressin plus albumin reported mortality and improved renal function.[28,30] One trial reported reversal of HRS.[30] The trials found no difference between treatments on mortality (12/30 versus 13/32; RR, 0.98; 95% CI, 0.54-1.78; I^2, 0%), reversal of HRS (10/20 versus 8/20; RR, 1.25; 95% CI, 0.63-2.5) or improvement in renal function (18/30 versus 21/32; RR, 0.90; 95% CI, 0.63-1.30; I^2, 0%).

The trial comparing bolus versus continuous administration of terlipressin plus albumin[29] found no differences in mortality (10/18 versus 11/19 patients; RR, 0.96; 95% CI, 0.55-1.69) or reversal of HRS (9/18 versus 14/19 patients; RR, 0.96; 95% CI, 0.55-1.69). Remaining outcome measures were not reported.

Discussion

The present review suggests that vasoconstrictor drugs alone or with albumin prolong short-term survival in type 1 HRS. Our subgroup analyses identified an effect on mortality at 15 days, but not at 30 days or beyond. The duration of the response should be considered when making treatment decisions and in the timing of liver transplantations. The improved survival seems related to an increased number of patients with reversal of HRS. On the other hand, the treatment also increases the risk of cardiovascular adverse events, including potentially serious events (such as myocardial infarction). Assessment of potential contraindications and close monitoring of adverse events seems essential.

The present review identified several methodological concerns in some trials, including unclear randomization and lack of sample size calculations and blinding. The number of patients included with type 2 HRS and the number of patients in trials on terlipressin alone or octreotide plus albumin was too small to make treatment

recommendations. Likewise, few patients were included in the trials comparing noradrenalin plus albumin versus terlipressin plus albumin or the trial comparing terlipressin administered as bolus or continuous infusion. None of these trials was designed to establish equivalence.

One of the main limitations of the present review is that only 376 patients were included. Identification of patients who clearly fulfill the diagnostic criteria for HRS is difficult, as is the recruitment of critically ill patients in clinical trials. Accordingly, the largest trials were multicentered and multinational. This increases the clinical heterogeneity as well as the external validity, making it possible to extrapolate the results to larger patient populations in similar specialized centers. Another important limitation of the present review is related to the methodological quality of the included trials. Our primary meta-analysis was not stable to sensitivity analyses of bias control. Unfortunately, we were unable to perform valid regression analyses to determine the risk of publication bias and other biases. The risk that such meta-regression analyses would be false-negative was considerable due to the limited number of trials in individual meta-analyses. Likewise, our results are unlikely to be stable to trial sequential analyses with adjustments for the multiple testing invariably associated with meta-analyses.[31] On the other hand, because we included mortality, the results were less susceptible to bias than subjective outcome measures.[22]

Three of the included trials compared different active treatment regimens.[28-30] Although the availability of noradrenalin and lower costs makes this treatment option interesting, the pharmacological effects of this drug are not identical to those of terlipressin. An assessment of whether noradrenalin and terlipressin have similar effects requires evidence from noninferiority or equivalence trials.[32,33] To demonstrate that the experimental treatment is not worse than the comparator, a pre-specified amount known as the noninferiority or equivalence margin should be defined. The margin should be included in the sample size calculations, and both intention-to-treat and per-protocol analyses should be performed. In accordance with previous epidemiological studies of clinical trials,[32,33] these basic requirements were not met in the trials from the present review. Accordingly, no conclusions regarding noninferiority or equivalence can be made.

For several of the included trials, sample size calculations were not reported. Accordingly, we were unable to determine whether sample size calculations were performed and the preset sample size achieved, the trials were terminated prematurely, or the trial was terminated at an arbitrary point. One of the included trials on terlipressin plus albumin versus albumin was terminated after an interim analysis suggested that 2,000 patients would be required to achieve adequate statistical power.[17] The specific criteria for the interim analysis were not clearly reported. The control group mortality rates for trials on terlipressin plus albumin were 63% to 100% compared with 83% for the trial terminated prematurely. We found little evidence of intertrial heterogeneity, and the mean control group Child-Pugh scores were remarkably similar (11 in three trials).[17-19] The trial with the highest mortality rate followed patients to the end of treatment, whereas the trial with the lowest mortality rate followed patients for 6 months.[16,19] Three trials found that baseline serum creatinine was an independent predictor of survival.[17-19] In our analyses, the baseline creatinine in the control groups of trials on terlipressin plus albumin ranged from 2.2 to 4.1 mg/dL (194-362 μmol/L). 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.[16] This may suggest that treatment should be administered early and that a protracted deterioration in renal function impedes recovery.

We originally planned to evaluate the effect of treatment on bridging to liver transplantation. Only one trial reported this outcome measure and found no difference between the treatment and control group.[19] However, following peer review comments pointing out the considerable differences between transplantation in different countries, we omitted this outcome measure. We considered performing a post hoc analysis to determine whether vasoconstrictor drugs decreased the number of patients who relapsed. However, the data were inconsistently reported. One trial only reported relapse rates for the treatment group.[17] A second trial did not report the relapse rates for both allocation groups, although the published report described that this outcome measure was assessed.[18] Considering the risk of reporting bias,[34] we decided not to perform this analysis.

The current diagnostic criteria for HRS includes presence of cirrhosis, ascites, serum creatinine $>$1.5 mg/dL or 133 μmol/L after at least 48 hours of diuretic withdrawal and volume expansion with albumin plus absence of shock, treatment with nephrotoxic drugs, and parenchymal renal disease.[3] The use of minor criteria and exclusion of patients with infections is abandoned. Type 1 HRS is now defined by renal failure with serum creatinine increasing to $>$2.5 mg/dL (226 μmol/L) within 2 weeks.[3] Type 2 HRS is defined by a moderate to slowly progressive renal failure with serum creatinine between 1.5 and 2.5 mg/dL (133-226 μmol/L). The trials in the present review used the previously established criteria.[1] The mean

serum creatinine in the trial finding the largest treatment effect was 194 μmol/L for the control group and 256 μmol/L for the treatment group, although only patients with type 1 HRS were included.[16] Whether the treatment effect is related to the diagnostic criteria remains to be established.

All trials in the present review excluded patients with important comorbidities. Still, terlipressin was associated with several adverse events, including abdominal cramps and diarrhea occurring in about 20%. The assessment of this adverse event may be difficult, because many patients received lactulose after developing hepatic encephalopathy. Cardiovascular adverse events occurred in about 6% of patients in the treatment group compared with no patients in the control group. The frequency is likely to be higher in unselected patient populations treated in everyday clinical practice. Accordingly, the monitoring of patients should include electrocardiography to detect cardiac ischemia or arrhythmia, especially in patients with hepatic encephalopathy or diabetes. Likewise, frequent observation to detect peripheral ischemia with cyanosis, livedo reticularis, or skin necrosis of the fingers or extremities is necessary. Patients should be informed of the potential adverse events to meet demands for informed consent.

Despite the treatments administered, the overall mortality when combining data on all patients treated with terlipressin plus albumin remained 57%. The discrepancy between survival rates and number of patients with reversal of HRS suggests that some patients may die despite improved renal function. Because we did not have individual patient data, we were unable to identify the cause of death in patients with improved renal function. Future trials may explore potential predictors of a beneficial response as well as phase IV studies to determine the treatment effect and risk of adverse events in nonspecialized units. The combined evidence suggests that additional trials are needed to further optimize the treatment of patients with HRS.

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