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ORIGINAL ARTICLE

Pharmacological treatment of hepatorenal syndrome: a network meta-analysis

Li Wang[1], Yin Long[2], Ke-Xin Li[3] and Gao-Si Xu[1,*]

[1]Department of Nephrology, The Second Affiliated Hospital of Nanchang University, Nanchang, Jiangxi, P. R. China; [2]Grade 2013, the Second Clinical Medical College of Nanchang University, Nanchang, Jiangxi, P. R. China; [3]Grade 2015, the Queen Mary College of Nanchang University, Nanchang, Jiangxi, P. R. China

*Corresponding author. Department of Nephrology, The Second Affiliated Hospital of Nanchang University, No. 1 Minde Road, Donghu District, Nanchang, Jiangxi 330006, P. R. China. Tel: +86-15079160103; Fax: +86-791-86311248; Email: gaosixu@163.com.

Abstract

Background: Observational studies suggest that hepatorenal syndrome (HRS) patients who receive pharmacological therapy before orthotopic liver transplantation display a post-transplant outcome similar to those without HRS. The aim of this study was to comprehensively compare and rank the pharmacological therapies for HRS.
Methods: We reviewed PubMed, Elsevier, Medline, and the Cochrane Central Register of Controlled Trials (CENTRAL) for studies that were published between 1 January 1999 and 24 February 2018. The primary endpoint was reversal of HRS. The secondary endpoints were the changes in serum creatinine (Scr) and serum sodium. We evaluated the different therapeutic strategies using network meta-analysis on the basis of Bayesian methodology.
Results: The study included 24 articles with 1,419 participants evaluating seven different therapeutic strategies for HRS. The most effective treatments to induce reversal of HRS were terlipressin plus albumin, noradrenaline plus albumin, and terlipressin, which had a surface under the cumulative ranking curve (SUCRA) of 0.086, 0.151, and 0.451, respectively. The top two treatments for decreasing Scr were dopamine plus furosemide plus albumin (rank probability: 0.620) and terlipressin plus albumin (rank probability: 0.570). For increasing serum sodium, the optimal treatment was octreotide plus midodrine plus albumin (rank probability: 0.800), followed by terlipressin plus albumin (rank probability: 0.544).
Conclusions: Terlipressin plus albumin and dopamine plus furosemide plus albumin should be prioritized for decreasing Scr in HRS, and octreotide plus midodrine plus albumin was the most effective at increasing serum sodium. Terlipressin plus albumin showed a comprehensive effect in both decreasing Scr and increasing serum sodium.

Key words: hepatorenal syndrome, network meta-analysis, terlipressin, dopamine, octreotide

Introduction

Hepatorenal syndrome (HRS) is a severe complication of advanced cirrhosis, characterized by renal failure and major disturbances in circulatory function. Renal failure in HRS is functional and caused by intense vasoconstriction of the renal circulation [1, 2]. HRS has a worse prognosis when there is rapidly progressive renal failure, leading to low survival expectancy [3–6].

Based on the existing literature [7–11], the main therapies for HRS can be roughly classified into four kinds according to disease progression: pharmacological prevention, transjugular intrahepatic portosystemic shunt (TIPS), orthotopic liver transplantation (OLT), and albumin dialysis. OLT remains the gold

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standard of therapy for HRS because of its ability to remove the core causes of this complication [12]. However, due to the shortage of donor organs and the extremely short survival, most patients with type 1 HRS die before receiving OLT [8]. By lowering the portal pressure, TIPS improves circulatory function and reduces the activity of vasoconstrictor systems in type 1 HRS [11]. Nevertheless, the procedure itself has risks, including bleeding, infection, and later deformation or narrowing of the shunt [13].

To date, the available pharmacological therapies are mainly pituitary analogs (terlipressin), alpha-adrenergic receptor agonists (norepinephrine and midodrine), and somatostatin analogs (octreotide). Terlipressin combined with albumin is currently the first-line treatment of HRS. Some researchers believe that norepinephrine is as safe and effective as terlipressin in patients with type 1 HRS, and norepinephrine is cheaper than terlipressin. Octreotide plus midodrine plus albumin is a newer, experimental therapy. By reviewing the papers from PubMed, Elsevier, Medline, and the Cochrane Central Register of Controlled Trials, we studied seven pharmacological therapies in randomized–controlled trials for HRS: noradrenaline plus albumin, terlipressin plus albumin, octreotide plus midodrine plus albumin, dopamine plus furosemide plus albumin, terlipressin, octreotide and placebo plus albumin, or albumin alone. However, the pharmacological therapies were compared with each other rather than with a placebo in most of the trials, which may have led to unreliable conclusions [14–17]. At this point, the network meta-analysis (NMA) is needed to make a direct or indirect comparison of the therapeutic effects on HRS between the seven pharmacological treatments.

NMA is known as a method of mixed or multiple treatment comparison in a single meta-analysis [18]. The multivariate approach allows one to 'borrow strength' across associated outcomes and potentially reduces the impact of reporting bias [19]. In the present article, we aimed to compare and rank the existing pharmacological strategies for HRS.

Methods

Search strategy and endpoint definitions

We reviewed relevant literature in electronic databases (PubMed, Elsevier, Cochrane Central Register, and Medline) published between 1 January 1999 and 24 February 2018. The search strategy was as follows: [hepatorenal syndrome] or [liver cirrhosis] or [syndrome, hepatorenal], [pharmacological prevention] or [pharmacological therapy] or [drug treatment], and [RCT] or [randomized controlled trial]. The relevant references were also reviewed for additional trials.

The primary endpoint was reversal of HRS at the end of the treatment period [defined as a decrease of 30% or greater in serum creatinine (Scr) level compared with the patient's baseline value to a final value of 1.5 mg/dL (133 μmol/L) or lower] (using binary variables). The secondary endpoints were the mean changes in Scr and serum sodium (using continuous variables).

Patients and inclusion criteria

Included studies met the following criteria: (i) only pharmacological therapy was studied; (ii) the duration of treatment was more than 5 days; (iii) two or more kinds of interventions were studied; and (iv) articles provided exact data of the reversal of HRS and the changes in Scr and serum sodium. Articles were excluded if they: (i) had duplicated records; (ii) had duplicated data; (iii) included nonpharmacological therapies; (iv) treated patients with TIPS, OLT, or albumin dialysis; (v) were ongoing or unpublished; or (vi) were published as conference proceedings or abstracts.

Cirrhosis was diagnosed based on clinical, biochemical, radiological, and/or histological criteria in all trials. HRS was diagnosed by using the criteria of the International Ascites Club [5]. The exclusion criteria of patients of these RCTs were generally as follows: (i) improvement in renal function after central blood volume expansion; (ii) bacterial infection associated with findings of systemic inflammation; (iii) use of nephrotoxic drugs; and (iv) history of coronary artery disease, obstructive cardiomyopathy, ventricular arrhythmia, or obliterative arterial disease of the limbs.

Data extraction

Data were extracted by two researchers independently according to the inclusion and exclusion criteria. Other indeterminacy or divergences were left to the third reviewer. The selection of process details is shown in Figure 1. Research settings included the first author's name, publication year, total number of participants, doses of intervention and control treatments, treatment duration, follow-up, and endpoint.

Study-quality assessment

The study-quality assessment was created by Review Manager (version 5.3; Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014). The risk was assessed according to four bias domains: selection, performance/detection, attrition, and reporting bias by using the bias-assessment tool.

Statistical analysis

The data were abstracted and analysed by using STATA [20] and the GeMTC and network packages in R software [21]. The odds ratio (OR) and corresponding 95% confidence interval (CI) were utilized to compare different medications with respect to the primary endpoint by using binary variables. The secondary endpoints were extracted from the included research and were used to measure the relative effect of various treatments by risk probability. Calculations in conventional meta-analyses were performed by using a random-effect model and the DerSimonian-Laird method in STATA. NMA was conducted in a Bayesian consistency-effect model assuming a continuous variable, which was executed using the GeMTC package in R software for Markov Chain Monte Carlo sampling. After a 5,000-sample burn-in for each chain, four parallel chains and 20,000 samples were obtained [22]. Convergence was checked using the Brooks-Gelman-Rubin diagnostic and trace plots [20, 21].

The rank probability and the contribution of each direct comparison in the network estimates were measured using the GeMTC and network packages in R software. Rank probability was defined as the probability that a treatment would rank in a certain spot. If a pharmacological therapy had a higher probability of ranking first than all the other therapies, then that therapy was considered the most effective one. The rank probability with respect to primary clinical outcome was obtained using the surface under the cumulative ranking curve (SUCRA). Thus, larger SUCRA scores indicated lower probabilities of the endpoint event. The publication bias was assessed via Deek's funnel-plot asymmetry and Egger's test [22].

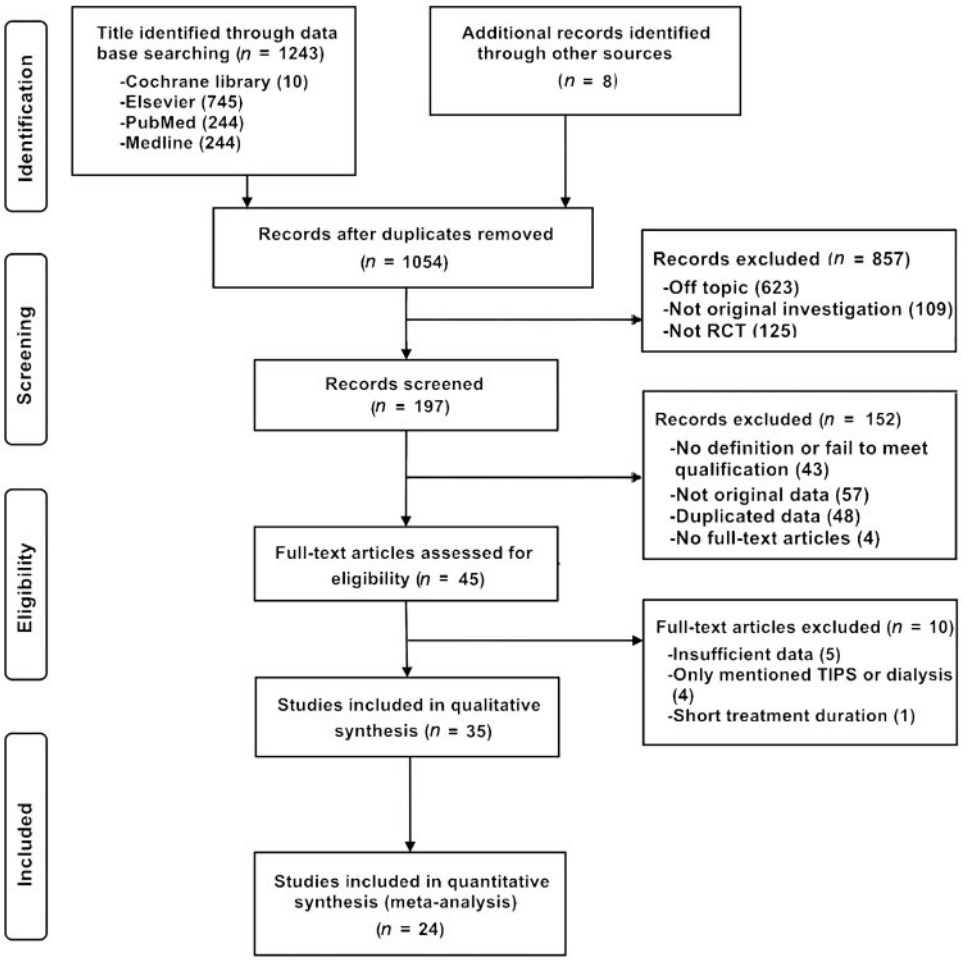

Figure 1. Flow diagram of the study-selection process

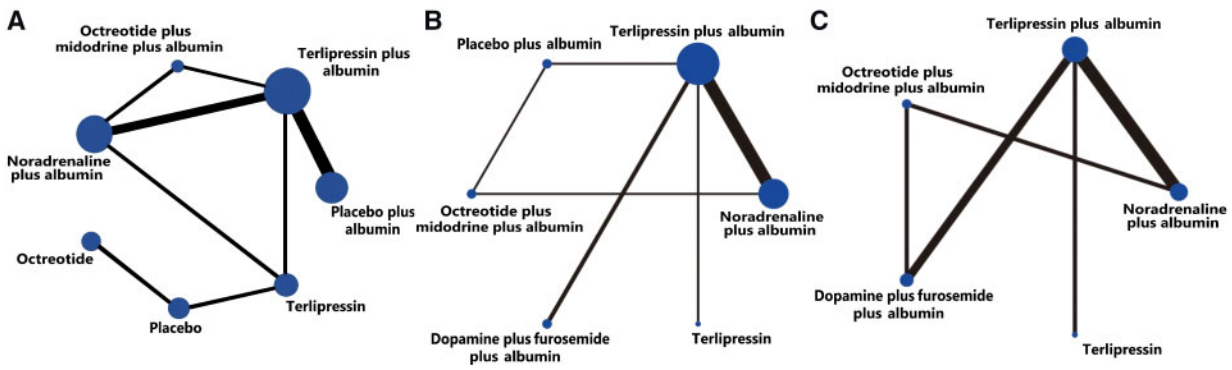

Figure 2. Treatment comparisons for NMAs
The size of the nodes is proportional to the total sample size of the treatment from all included trials. Directly comparable treatments are linked with a line, the thickness of which is proportional to the total sample size for assessing the comparison.

Results

Description of the included studies

A total of 1,243 articles were identified, of which 24 clinical trials with 1,419 participants were ultimately included (Figure 1). The results of these studies were published between 1999 and 2016. Among the 24 studies, 16 investigated the endpoint event of reversal of HRS and 12 provided data on decreasing Scr and increasing serum sodium; 4 studies provided data about both endpoint events. The number of patients included in every study ranged from 6 to 99 and the follow-up for patients ranged from 15 to 100 days.

The quality of the included articles was modest overall. All studies were prospective RCTs: two were open-label trials,

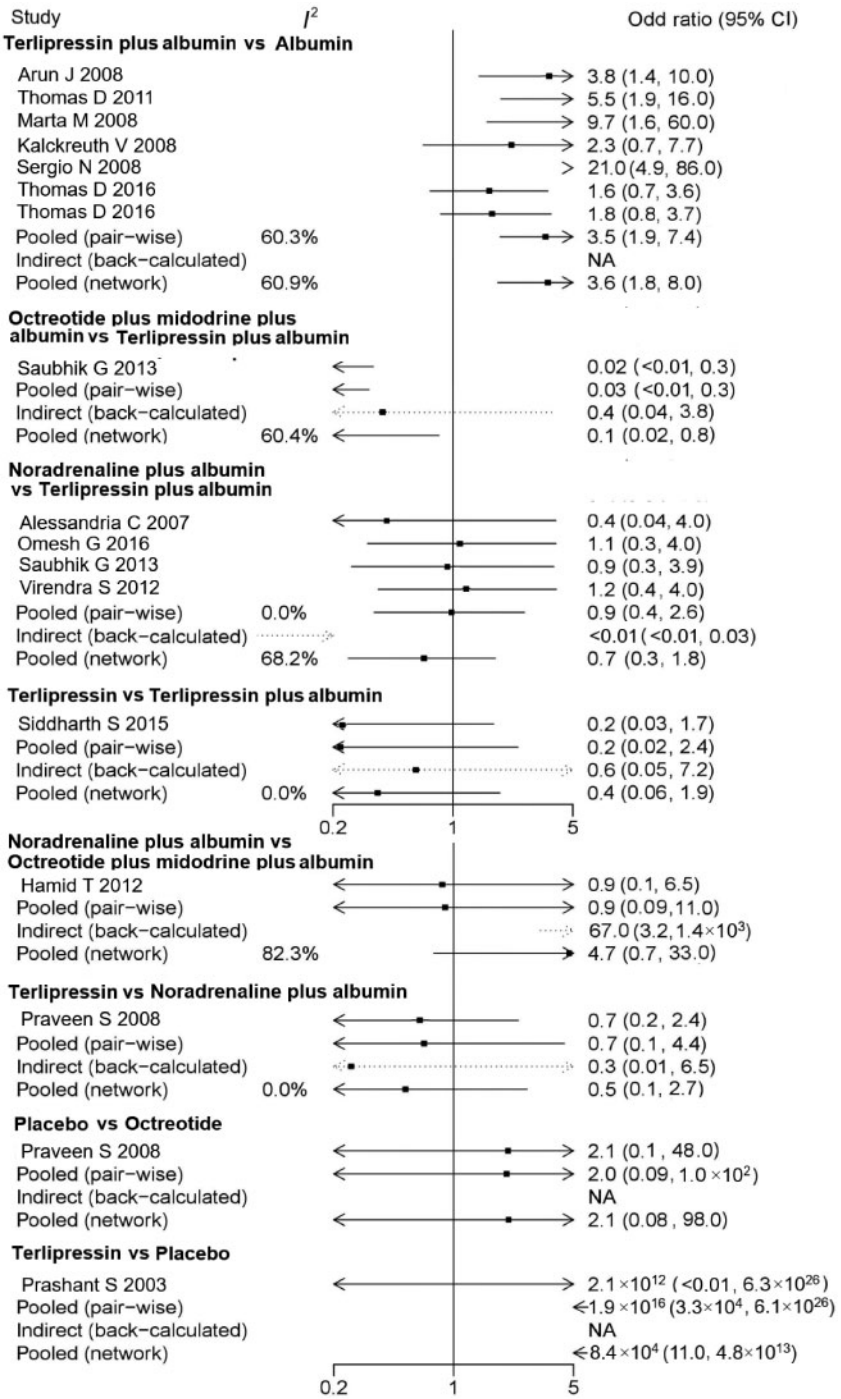

Figure 3. The results of direct comparisons and heterogeneity analyses on endpoints

four were double-blind trials, and the others were also blind but not explicitly stated as single-blind or double-blind. All trials had two arms. The dose of albumin was almost the same (20 g/day). The treatment duration was approximately 15 days.

The funnel plots of the included records appeared symmetrical [23], which corresponded to the results of Egger's test (Scr group: $P = 0.110$, Coef = 9.38, 95% CI −2.61 to 21.37; serum-sodium group: $P = 0.136$, Coef = 4.40, 95% CI −1.85 to 10.66), leaving the publication bias insignificant.

Exploration of network-structure, heterogeneity, consistency, and sensitivity analyses

Network plots of treatment comparisons for Bayesian NMA are shown in Figure 2. There were six interventions for reversal of HRS (Figure 2A), six for Scr (Figure 2B), and five for serum sodium (Figure 2C). The sizes of the nodes (blue circles) correspond to the sample sizes of the interventions. The comparisons were connected by a straight line, of which the thickness corresponds to the number of trials that assessed the

Table 1. Sensitivity analyses on endpoints

Treatment strategy	Standard analysis ($n = 16$)	Excluding 2 trials with the smallest sample size ($n = 14$)	Excluding 2 trials with the length of follow-up more than 100 days ($n = 12$)	Excluding 2 trials with the length of follow-up less than 15 days ($n = 10$)	Excluding 3 trials without detailed dose of treatments ($n = 7$)
Noradrenaline plus albumin	**5.3×10^8 (22, 9.4×10^{28})**	**5.4×10^8 (22, 9.4×10^{28})**	**5.6×10^8 (26, 1.4×10^{29})**	**4.9×10^8 (26, 1.6×10^{27})**	**6.3×10^8 (11, 1.3×10^{29})**
Terlipressin plus albumin	**8.1×10^8 (32, 4×10^{29})**	**8.1×10^8 (34, 5.9×10^{29})**	**7.9×10^8 (34, 5.7×10^{29})**	**7.4×10^8 (37, 6.2×10^{29})**	**6.9×10^8 (17, 4.4×10^{29})**
Octreotide plus midodrine plus albumin	**1.2×10^8 (3.9, 2.1×10^{28})**	**1.6×10^8 (3.8, 2.6×10^{28})**	**1.2×10^8 (4.1, 1.6×10^{28})**	**1.1×10^8 (4.1, 1.6×10^{28})**	**1.5×10^8 (5, 1.6×10^{28})**
Placebo plus albumin	**2.3×10^8 (8.1, 3.8×10^{28})**	**3.0×10^8 (19, 6.1×10^{28})**	**2.2×10^8 (14, 4.2×10^{28})**	**2.0×10^8 (10, 1.6×10^{28})**	**2.1×10^8 (11, 1.3×10^{28})**
Terlipressin	**3.0×10^8 (13, 5.2×10^{28})**	**3.7×10^8 (27, 3.3×10^{28})**	**2.9×10^8 (21, 6.0×10^{28})**	**2.6×10^8 (14, 5.3×10^{28})**	**6.9×10^8 (17, 1.3×10^{28})**
Octreotide	0.50 (0.01, 13)	0.50 (0.01, 14)	0.47 (0.0088, 12)	0.48 (0.0094, 12)	0.47 (0.0096, 12)
Placebo	Reference	Reference	Reference	Reference	Reference

Data are presented as odds ratio (95% CI). All risk ratios use placebo as referenced agent. Significant results are in bold. There were no important changes in the remaining results, which showed low sensitivity and satisfactory stability.

comparison. As shown in the network plot, the number of interventions varied between subjects.

A total of 50,000 iterations were increased to obtain satisfactory convergence. The results of available direct comparisons and heterogeneity analyses are shown in Figure 3. Pairwise and NMA estimates were similar in magnitude and testing did not reveal evidence of inconsistency between direct and indirect treatment effects ($P > 0.05$). There was no sign of global inconsistency in any network.

After the sensitivity analyses, terlipressin plus albumin still ranked as the top treatment. There were no important changes in the remaining results, which showed low sensitivity and satisfactory stability (Table 1).

Primary outcomes—reversal of HRS

Compared with placebo, the significantly effective treatments that induced reversal of HRS with moderate- to high-quality evidence were terlipressin plus albumin, noradrenaline plus albumin, terlipressin alone, albumin with placebo or albumin alone, and octreotide plus midodrine plus albumin [OR of 8.1×10^8 (95% CI, 32–1.4×10^{29}), 5.3×10^8 (95% CI, 22–9.4×10^{28}), 3.0×10^8 (95% CI, 13–5.2×10^{28}), 2.3×10^8 (95% CI, 8.1–3.8×10^{28}), and 1.2×10^8 (95% CI, 3.9–2.1×10^{28}), respectively]. There was no significant difference between placebo and octreotide (OR, 0.5; 95% CI, 0.01–13).

Terlipressin plus albumin and noradrenaline plus albumin were most likely to be ranked the best and second best (SUCRA of 0.086 and 0.151), respectively. They were followed by terlipressin alone, albumin with placebo or albumin alone, and octreotide plus midodrine plus albumin (SUCRA of 0.451, 0.464, and 0.576, respectively). Placebo and octreotide were ranked as the least effective treatments (SUCRA of 0.862 and 0.911, respectively; Figure 4).

Secondary outcomes—the changes in Scr and serum sodium

The change in Scr

The decrease in the Scr level in patients treated with terlipressin plus albumin was greater than that in the patients treated with placebo plus albumin (OR, 2.2×10^2; 95% CI, 1.1×10^2–3.2×10^2) and terlipressin alone (OR, 1.9×10^2; 95% CI, 53–3.2×10^2).

The results of rank probability showed that dopamine combined with furosemide and albumin was most likely to be ranked the best (rank probability: 0.620), followed by terlipressin plus albumin (rank probability: 0.570), noradrenaline plus albumin (rank probability: 0.576), octreotide plus midodrine plus albumin (rank probability: 0.686), and terlipressin alone (rank probability: 0.440); placebo plus albumin was the least effective treatment (rank probability: 0.657), as shown in Table 2.

The change in serum sodium

The increase in serum sodium in patients treated with terlipressin plus albumin (OR, −7; 95% CI, −12 to −1.7) was greater than that in patients treated with terlipressin alone.

We further investigated the role of the different therapeutic strategies in serum-sodium variation and the results showed that octreotide plus midodrine plus albumin was the best (rank probability: 0.798), followed by terlipressin plus albumin (rank probability: 0.544), dopamine combined furosemide with albumin (rank probability: 0.332), noradrenaline plus albumin (rank probability: 0.541), and terlipressin alone (rank probability:

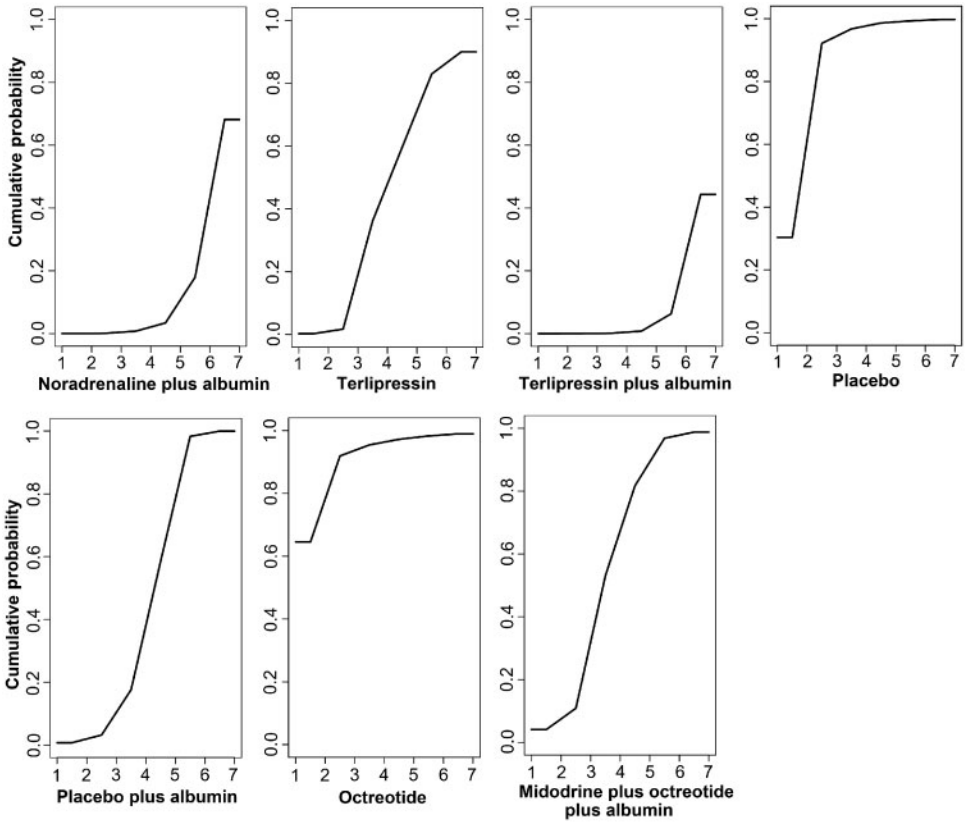

Figure 4. The drug's efficacy measured by SUCRA probabilities
The drug's efficacy measured by SUCRA values normalized to %, ordered from the least to the most, was terlipressin plus albumin (8.60), noradrenaline plus albumin (15.1), terlipressin alone (45.1), albumin (46.4), octreotide plus midodrine plus albumin (57.6), placebo (86.2), and octreotide (91.1).

Table 2. The rank probabilities of pharmacological therapies on decreasing serum creatinine and increasing serum sodium

Pharmacological therapy	Rank 1	Rank 2	Rank 3	Rank 4	Rank 5	Rank 6
Serum creatinine						
NPA	0.134	0.264	**0.576**	0.024	0.002	<0.001
TPA	0.232	**0.570**	0.187	0.010	<0.001	<0.001
OMA	0.009	0.011	0.027	**0.686**	0.241	0.026
DPF	**0.620**	0.147	0.197	0.026	0.005	0.001
TER	0.004	0.005	0.011	0.225	**0.440**	0.315
PPA	<0.001	<0.001	0.002	0.029	0.310	**0.657**
Serum sodium						
NPA	0.031	0.092	0.312	**0.541**	0.024	NA[a]
TPA	0.150	**0.544**	0.276	0.029	<0.001	NA[a]
OMA	**0.798**	0.101	0.061	0.029	0.012	NA[a]
DPF	0.017	0.254	**0.332**	0.349	0.048	NA[a]
TER	0.005	0.009	0.019	0.052	**0.915**	NA[a]

The bold rank probability was bigger than other rank probabilities in the same row. Therefore, the rank corresponding to the bold font represents the ranking of the effect of pharmacological therapies on decreasing serum creatinine and increasing serum sodium.
NPA, noradrenaline plus albumin; TPA, terlipressin plus albumin; OMA, octreotide plus midodrine plus albumin; DPF, dopamine plus furosemide; TER, terlipressin; PPA, placebo plus albumin.
[a]Only five pharmacological therapies for increasing serum sodium were included and the 'rank 6' did not exist.

0.915), as shown in Table 2. In contrast to the ranking of strategies for Scr, octreotide plus midodrine plus albumin was ranked the best for serum sodium, whereas dopamine plus furosemide plus albumin fell to the third and the rank of terlipressin plus albumin was unchanged.

Discussion

The effectiveness and safety of HRS pharmaceutic treatments have been repeatedly emphasized and their clinical application in HRS management remains preliminary [24]. The most important goal of medication is to reduce the occurrence rate of a

disease and allow patients to receive other treatments, such as OLT. A recent case–control trial showed that patients with HRS who received medication before OLT showed similar 3-year survival probability, the incidence of impairment of renal function, severe infections, acute rejection, days in Intensive Care Unit, days in hospital, and transfusion requirements after transplantation compared with patients without HRS [25].

Since the included articles provide different types of data, we used the HRS reversal rate (binary variables) and the average change in Scr (continuous variables) to assess the effect of each drug strategy on renal function. Our current NMA found that terlipressin plus albumin and dopamine plus furosemide plus albumin were superior to other pharmacological strategies in the reversal of Scr. As a new analog, terlipressin does not have the adverse effects of traditional vasopressin analogs, mainly severe ischemic complications. Administration of low-dose dopamine enhances creatinine clearance and improves splanchnic blood flow distribution through the action of β2 adrenergic receptors [26], which may explain why dopamine combined with furosemide and albumin showed better effects in reducing Scr.

HRS is usually associated with diluting-style hyponatremia. When the serum sodium is lower than 130 mmol/L, the occurrence rate of HRS in patients with hyponatremia is also increased [27]. Increasing serum sodium contributes to the restoration of hemodynamics. OLT is the ultimate solution for HRS and the prognosis of HRS is associated with the time of OLT [28–30]. Hyponatremia is closely related to survival rates after OLT. In recent years, some scholars have combined the model for end-stage liver disease (MELD) with serum sodium to establish MELD-Na. This model predicts that survival rate of patients with cirrhosis after TIPS and OLT is better than that of patients with MELD [31]. Therefore, we observed the effects of drugs on serum sodium. Our current NMA results showed that octreotide plus midodrine plus albumin increased serum sodium the best. The combination of an arterial vasoconstrictor (midodrine) and a glucagon inhibitor (octreotide) can increase the effectiveness of the former in the treatment of HRS [32]. Octreotide has been shown to be effective in reducing visceral hyperemia and portal pressure [32–35], but it can also increase the mean arterial pressure in patients with cirrhosis [32].

One meta-analysis on terlipressin vs other vasoactive drugs made head-to-head comparisons of the drug treatments (terlipressin vs noradrenaline, terlipressin vs midodrine and octreotide, or terlipressin vs dopamine) [36]. Our study compared multiple drugs together and ranked the efficacy of multiple drugs. The earlier meta-analysis was based on other vasoactive drugs (noradrenaline, midodrine and octreotide, and dopamine) as a whole and concluded that terlipressin significantly reversed HRS compared with other vasoactive drugs [36]. However, the effect of different vasoactive drugs on reversing HRS was inconsistent. For example, terlipressin was superior to octreotide alone, but there was no difference between terlipressin and noradrenaline in reversing HRS.

Few RCTs with pharmacological therapies for HRS have been published at present. The sample size of the present study was still relatively small, which caused a larger range of 95% CI of our analysis; therefore, it is difficult to estimate the reliability of the conclusions.

Terlipressin plus albumin has become the first-line treatment of type 1 HRS and our study also suggested that terlipressin plus albumin was the best pharmacological therapy for HRS so far. However, the relatively high cost of the drug makes it less practical for use in many countries, especially over long periods of time. Terlipressin is only effective in one-third to one-half of patients with type 1 HRS. Therefore, the choice of second-line treatment options for terlipressin-ineffective patients is a problem that needs to be solved. It is worth mentioning that no significant difference was observed between norepinephrine plus albumin and terlipressin plus albumin, and this result was similar to the existing meta-analysis findings [7, 14, 37]. Norepinephrine is easier to obtain and costs less than terlipressin. Therefore, norepinephrine plus albumin might also be a good choice. There might be more treatments that have similar effects to terlipressin plus albumin, which requires more relevant RCTs to discover.

In conclusion, the current analysis recommended that terlipressin plus albumin and dopamine plus furosemide plus albumin should probably be prioritized in Scr reversal in HRS and that octreotide plus midodrine plus albumin was the most effective in increasing serum sodium. Terlipressin plus albumin showed a comprehensive effect in both decreasing Scr and increasing serum sodium. However, the impact of pharmacological therapies on HRS and the mortality rate need to be further assessed.

Authors' contributions

L.W. and Y.L. performed the literature searching, reviewed articles, completed the data analysis using STATA, WinBUGS, R software using 'gemtc' package and 'network' package, and drafted the manuscript. K.X.L. reviewed the articles and provided the second views during the manuscript preparation. G.S.X. designed the analysis and revised the manuscript. All the authors read and approved the final version of the manuscript.

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Not applicable.

Conflicts of interest

The authors declare that there is no conflict of interest.

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