Comparative efficacy of vasoconstrictor therapies for type 1 hepatorenal syndrome: a network meta-analysis

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ABSTRACT

Introduction: The outcome of a comparative efficacy and safety of vasoconstrictor therapies for treatment of patients with type 1 hepatorenal syndrome (HRS-1) remain inconclusive.

Areas covered: We searched literature databases for randomized controlled trials (RCTs) until 31 January 2016, and included ten eligible RCTs. In conclusion, terlipressin was the most efficacious vasoconstrictor drug for HRS-1, but had a higher probability of causing AEs. Norepinephrine was an attractive alternative to terlipressin and associated with less AEs.

Expert commentary: To date, most previous traditional meta-analyses included trials with a limited population and compared terlipressin alone or with albumin against no intervention or albumin. Since different HRS types have different diagnoses and show different responses to vasoconstrictors, it may be questionable to combine data from patients with type 1 and type 2 HRS, which has been reported for most previous meta-analyses. Thus, performing a high-quality network meta-analysis of the existing literature is a valuable way to interrogate published data and to draw conclusions which may inform on the best interventional strategy.

1. Introduction

Hepatorenal syndrome (HRS) is a functional renal impairment that occurs in approximately 7–15% of patients with advanced cirrhosis and ascites and is classified as type 1 and type 2 [1]. Hepatorenal syndrome type 1 (HRS-1) is characterized by a progressive and rapid deterioration of renal function, usually accompanied by multiorgan failure [2]. Compared with type 2 HRS, HRS-1 is more severe with a doubling of the initial serum creatinine level greater than 2.5 mg/dl along with decreased urine output, occurring rapidly and in less than 2 weeks with typical features suggestive of multiorgan dysfunction. Without treatment, the prognosis of HRS-1 is poor, with a mortality as high as 83% within 3 months and a median survival of only 2 weeks [2,3].

The use of vasoconstrictor drugs in combination with albumin may ameliorate peripheral and splanchnic vasodilation to attenuate renal vasoconstriction and restore renal perfusion, which is also a bridging option to reverse HRS-1 and improve survival of patients who are awaiting liver transplantation [4,5]. Terlipressin as a vasopressin analog was introduced as an alternative to vasopressin treatment as it is associated with a reduced incidence of side effects. Moreover, the side effects of terlipressin can be minimized when delivered to the patient as a continuous infusion [6]. Several pairwise meta-analyses confirmed that the use of terlipressin in conjunction with albumin could improve renal function and increase median survival time [7–9]. Subsequent Cochrane meta-analyses showed that the initial randomized controlled trials (RCTs) included an evaluation of the efficacy of terlipressin in crossover designs and were of small sample size with a short treatment duration [10,11]. Furthermore, terlipressin is not yet approved by the US FDA, unavailable in many countries, and the cost may prohibit use in some countries where it has been approved [9]. Norepinephrine, a catecholamine with predominately alpha-adrenergic activity, is a valid alternative to terlipressin, shows encouraging clinical efficacy, is more widely used, and has a reduced cost. In addition, midodrine combination with octreotide, a long-acting analog of somatostatin, can also increase short-term survival associated with reduced adverse events (AEs) in the treatment for HRS-1 [2]. However, although some clinical trials were able to demonstrate greater efficacy of these vasoconstrictor drugs with albumin when compared with albumin alone, the comparative efficacy and safety of these vasoconstrictors is largely unknown as evaluated by traditional meta-analysis, with a lack of evidence from head-to-head clinical trials. Moreover, since different HRS types have...
different diagnoses and exhibit different responses to vasoconstrictors, it may be questionable to combine data from patients with HRS-1 and type 2 HRS in most previous meta-analyses [12,13]. Additionally, most trials conducted pairwise comparisons and only compare the effect of one intervention or no intervention against terlipressin in a limited population. Therefore, no conclusive evidence is currently available from a systematic evaluation of the comparative efficacy and safety of vasoconstrictors in the treatment of HRS-1 patients.

Theoretically, large-scale head-to-head RCTs with multiple comparator arms should be conducted to resolve the above issues. However, it is infeasible that all available vasoconstrictors are evaluated in a single trial. On that basis, we applied established methodology used in network meta-analysis to integrate direct and indirect comparisons for simultaneous comparisons of all investigated treatments. In view of the limitations of previous studies, the aim of our study was to summarize a much broader evidence base and to jointly compare the main clinical outcomes and safety profile with three major vasoconstrictor therapies (terlipressin, norepinephrine, midodrine plus octreotide) for patients with HRS-1.

2. Methods

2.1. Search strategy

This systematic review was reported according to the preferred reporting items of systematic reviews and meta-analysis (PRISMA) statement [14]. We identified studies published up to 31 June 2016, comparing different vasoconstrictor drugs for treatment of HRS-1 by searching the following electronic databases: PubMed, Embase, and Cochrane Central Register of Controlled Trials with the key terms ‘hepatorenal syndrome, vasoconstrictor, terlipressin, norepinephrine, midodrine, octreotide, vasopressin, noradrenaline, omipressin.’ Trials included were restricted to RCTs and there was no language restriction. We manually searched bibliographies of retrieved articles, relevant meta-analyses, and systematic reviews.

2.2. Selection criteria

Eligible trials should meet the following criteria: (1) prospective RCTs estimating the efficacy and safety of vasoconstrictor regimens for the treatment of adult patients with HRS-1; (2) treatment and control groups including vasoconstrictor drugs alone or with albumin versus no intervention or with albumin, vasoconstrictor drugs alone or with albumin versus placebo alone or with albumin, and comparisons of different vasoconstrictor drugs with or without albumin; (3) reporting at least one outcome and sufficient data on the primary and secondary outcomes for HRS-1 in each group; and (4) vasoconstrictor therapy given for more than 3 days.

Not eligible for inclusion: (1) studies considered as retrospective or prospective cohort studies, crossover or non-randomized design, case reports, reviews, and conference reports; (2) trials with comparisons of vasoconstrictors versus other vasoactive drugs; and (3) the proportion of HRS-1 patients is unclear in some trials containing patients with two types of HRS.

2.3. Assessed outcomes

The primary outcome was the reversal of HRS, defined as decrease of serum creatinine to a value of 133 μmol/l (1.5 mg/dl) or lower during treatment. Secondary outcomes included mortality (all cause) or liver transplantation (MOLT) and AEs.

2.4. Data extraction

Two investigators (Yi-Jing Han and Tian-Tian Zou) abstracted data independently from each study. A standard form was designed to prompt data extraction from each study. Abstracted data included first author’s last name, geographic location of study, year of publication, details of the study design, number of participants, population characteristic, treatment dose and duration, duration of follow-up, definition of reversal of HRS, and outcomes (reversal of HRS, MOLT, and AEs). The observation arm specifically referred to placebo plus albumin or albumin alone. Discrepancies related to data extraction were resolved by another investigator (Ming-Hua Zheng). In addition, in case several publications overlapped, only the study with the most detailed or most recent content was included. When some data or relevant information was unavailable and needed for the analyses, we contacted original authors for assistance and clarifications by email.

2.5. Quality assessment

To access the risk of bias, two investigators (Ji-Na Zheng and Tian-Tian Zou) independently evaluated methodologic quality using the Cochrane risk of bias assessment tool. This tool includes the following items: adequate sequence generation, allocation concealment, blinding, incomplete data, selective reporting, and other sources of bias [15]. Trials with high or unclear risk for bias for any one of the first three components were considered as trials with high risk of bias. Otherwise, they were regarded as trials with low risk of bias. When any discrepancies arose, another reviewer (Yi-Jing Han) was consulted.

2.6. Data analysis

We performed traditional pairwise meta-analysis and network meta-analysis with random-effects model to calculate 95% confidence intervals (CIs) and pooled estimates of odds ratios (ORs) or hazard ratios (HRs) for primary and secondary outcomes. A random-effects model was used due to the anticipated variability between trials in terms of patient populations, interventions, and concomitant interventions. Moreover, an I² value greater than 50% indicates significant heterogeneity. A random-effects model was used in the case of significant heterogeneity (I² > 50%). Additionally, we used node-splitting method to estimate the inconsistency of the model and reported Bayesian P value between the direct and indirect evidence. To rank the vasoconstrictors for an outcome, we used surface under the cumulative ranking (SUCRA) probability, which present as a percentage the efficacy or safety of every intervention that is always best without
uncertainty [16]. Statistical theories and methods of pairwise meta-analysis and network meta-analysis were detailed in our previous publication [17–19].

3. Results

3.1. Study characteristics

The PRISMA flowchart summarizing the process of electronic searching is shown in the Supplementary Figure 1. We identified 2009 studies through title and abstract screening and 1998 studies were excluded after further assessment of the full text. Finally, 11 studies with a total of 685 patients were available for network meta-analysis. The diagnosis of HRS was based on the International Club of Ascites criteria [1,20]. The duration of treatment ranged from 14 days to 6 month and the mean age of the patients was 54 (ranged from 34 to 75). We included three vasoconstrictor drugs according to eligible studies: terlipressin, norepinephrine, and midodrine plus octreotide. All studies were RCTs with two arms and the mean follow-up after vasoconstrictor drugs was 108 days (ranged from 30 to 180). For the primary outcome of interest, 4 unique comparisons were available for 10 different trials on reversal of HRS [21–30], 9 trials in progression of MOLT [10,21,23,24,26–30], while for AEs, there were 6 trials providing available data for 4 unique comparisons [23,24,27–30]. Table 1 represents the characteristics of the included trials. Quality assessment of RCTs was evaluated by the Cochrane risk of bias tool showing in Supplementary Figure 2, which suggested low-to-moderate risk of bias. Networks of eligible comparisons of the primary and secondary outcomes are presented in Figure 1. Overall moderate heterogeneity (Figures 2 and 3) is existed in this meta-analysis.

3.2. Reversal of HRS

Figure 2(a) shows the results of the network meta-analysis alongside pairwise meta-analysis using ORs with 95% CIs on the primary outcome of reversal of HRS to allow direct checks for consistency of results, which also combined both numerical estimates and forest plot. As the shown in the summary forest plot matrix, terlipressin significantly provided a more favorable outcome than observation (ORs 0.24, 95% CIs 0.07–0.65) and midodrine plus octreotide (0.17, 0.02–1.15). Although statistical significance was not reached for terlipressin versus norepinephrine, there was a tendency that terlipressin was superior to norepinephrine (0.97, 0.25–3.73) and other vasoconstrictors. The SUCRA probability was also presented for each intervention along the diagonal; terlipressin had the highest probability (83%) as the best vasoconstrictor option on reversal of HRS followed closely by norepinephrine with the second highest probability (80%).

3.3. Mortality or liver transplantation

All nine trials reported available information on MOLT and were included for meta-analysis. Figure 4 presents relative effect of vasoconstrictor treatments using HRs with 95% CIs and forest plot. Although the difference was not statistically significant for all vasoconstrictor drugs, compared with observation, there was a trend that terlipressin (HRs 0.60, 95% CIs 0.25–1.10) was associated with a decreased risk of MOLT compared to norepinephrine (0.64, 0.18–1.90) and midodrine plus octreotide (0.68, 0.13–2.60). The SUCRA probability of increased risk of MOLT is also presented in Figure 4. MOLT is a negative outcome, which is different from the positive outcome of reversal of HRS. Therefore, even if observation had the great probability (83%), which was the most ineffective vasoconstrictors in reducing the risk of MOLT, conversely, terlipressin had the lowest probability (29%) for being the most effective vasoconstrictor in reducing the risk of MOLT.

3.4. Adverse events

Figure 2(b) illustrated the ORs with 95% CIs and summary forest plot for AEs obtained for traditional pairwise and network meta-analyses. Following Figure 2(b) from left to right, although comparisons showed no statistical significance, there was a trend that terlipressin was more likely to cause AEs than observation (ORs 0.43, 95% CIs 0.11–1.77), norepinephrine (0.63, 0.10–4.38), and midodrine plus octreotide (1.04, 0.12–7.21). Along the diagonal, the SUCRA probability of each vasoconstrictor drug is represented in Figure 2(b). Terlipressin had the highest probabilities (70%) of reduction in AEs, indicating terlipressin was associated with an increased risk of AEs than from remaining treatments. Additionally, midodrine plus octreotide (66%) showed the highest probability for being in the second ranking positions.

3.5. Comparisons between traditional pairwise and network meta-analyses

Figures 2 and 3 show results of traditional pairwise and Bayesian network meta-analyses to aid visual assessment of consistency between the two analyses. Although the pooled estimates showed small differences, the CIs from two analyses overlapped for the majority of our results. In addition, we evaluated the inconsistency of our results using node-splitting method and Bayesian P values. The node-splitting method could separate the evidence concerning certain comparison into direct and indirect evidence, and the inconsistency was reported by its Bayesian P value in Figure 5. In general, the P values and node-splitting method showed no significant inconsistency within the networks for any of the three outcomes.

4. Discussion

In this network meta-analysis, we systematically reviewed the efficacy and safety of current vasoconstrictor treatments available in RCTs for patients with HRS-1, including terlipressin, norepinephrine, and midodrine plus octreotide. As illustrated in our results, although the difference of pooled and indirect comparisons between the included interventions was not statistically significant, we demonstrated graphical representations of SUCRA probability indicating the probability that a given intervention is first, second, third best, and so on when compared with all other interventions in the network. As a
<table>
<thead>
<tr>
<th>Author</th>
<th>Country</th>
<th>Mean age</th>
<th>Treatment/Control</th>
<th>Serum creatinine (mg/dl)</th>
<th>MELD score</th>
<th>Dose</th>
<th>Duration</th>
<th>Follow-up (days)</th>
<th>Study size</th>
<th>HRS reversal</th>
<th>Treatment/Control</th>
<th>Mortality or liver transplantation</th>
<th>Adverse events Treatment/Control</th>
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<tr>
<td>Boyer (2016) [23]</td>
<td>American</td>
<td>55</td>
<td>TP/OBS</td>
<td>3.6 ± 1.1/3.7 ± 1.1</td>
<td>33.5 ± 6.2/32.6 ± 5.5</td>
<td>TP: 1 mg every 6 h/OBS: 1 mg every 6 h</td>
<td>14 days</td>
<td>90</td>
<td>196</td>
<td>23/15</td>
<td>44/47</td>
<td>53/30</td>
<td></td>
</tr>
<tr>
<td>Martin-Llahí Í (2008) [25]</td>
<td>Spain</td>
<td>57</td>
<td>TP/OBS</td>
<td>3.6 ± 1.4/4.0 ± 2.4</td>
<td>30 ± 9/28 ± 8</td>
<td>TP: 1–2 mg every 4 hours/OBS: NR</td>
<td>3 months</td>
<td>90</td>
<td>35</td>
<td>6/2</td>
<td>NR</td>
<td>NR</td>
<td></td>
</tr>
<tr>
<td>Neri (2007) [26]</td>
<td>Italy</td>
<td>59</td>
<td>TP/OBS</td>
<td>2.8 ± 1.1/2.8 ± 1.2</td>
<td>NR</td>
<td>TP: 1 mg every 8 h/OBS: NR</td>
<td>6 months</td>
<td>120</td>
<td>52</td>
<td>21/5</td>
<td>12/21</td>
<td>NR</td>
<td></td>
</tr>
<tr>
<td>Sanyal (2008) [27]</td>
<td>American</td>
<td>52</td>
<td>TP/OBS</td>
<td>3.9 ± 2.2/3.8 ± 1.2</td>
<td>33.4 ± 6/33.4 ± 6.3</td>
<td>TP: 1 mg every 6 h/OBS: 1 mg every 6 h</td>
<td>6 months</td>
<td>180</td>
<td>112</td>
<td>19/7</td>
<td>32/35</td>
<td>18/12</td>
<td></td>
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<tr>
<td>Solanki (2003) [10]</td>
<td>India</td>
<td>52</td>
<td>TP/OBS</td>
<td>2.9 ± 0.1/2.2 ± 0.2</td>
<td>NR</td>
<td>TP: 2 mg daily/OBS: NR</td>
<td>15 days</td>
<td>NR</td>
<td>24</td>
<td>NR</td>
<td>7/12</td>
<td>NR</td>
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</tr>
<tr>
<td>Alessandria (2007) [21]</td>
<td>Italy</td>
<td>56</td>
<td>TP/NE</td>
<td>2.5 ± 0.3/2.3 ± 0.2</td>
<td>26 ± 2/26 ± 1</td>
<td>TP: 1 mg every 4 h/NE: 1 mg every 4 h</td>
<td>6 months</td>
<td>39</td>
<td>9</td>
<td>4/3</td>
<td>5/4</td>
<td>NR</td>
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<tr>
<td>Sharma (2008) [28]</td>
<td>India</td>
<td>48</td>
<td>TP/NE</td>
<td>3.0 ± 0.5/3.3 ± 1.3</td>
<td>29.6 ± 6.2/31.6 ± 6.0</td>
<td>TP: 0.5–2 mg every 6 h/NE: 0.5–3 mg every hour</td>
<td>15 days</td>
<td>NR</td>
<td>40</td>
<td>11/11</td>
<td>9/9</td>
<td>5/3</td>
<td></td>
</tr>
<tr>
<td>Singh (2012) [29]</td>
<td>India</td>
<td>50</td>
<td>TP/NE</td>
<td>3.1 ± 0.7/3.3 ± 0.7</td>
<td>26.39 ± 3.1/24.65 ± 5.31</td>
<td>TP: 0.5–2 mg every 6 h/NE: 0.5–3 mg every hour</td>
<td>14 days</td>
<td>30</td>
<td>46</td>
<td>9/10</td>
<td>16/15</td>
<td>0/0</td>
<td></td>
</tr>
<tr>
<td>Cavallin (2015) [24]</td>
<td>Italy</td>
<td>63</td>
<td>TP/MID + OCT</td>
<td>3.6 ± 1.0/3.8 ± 2.1</td>
<td>31.2 ± 5.8/29.1 ± 8.1</td>
<td>TP: 3 mg every 24 h/MID: 7.5 mg every 8 h/OCT: 100 Gg every 8 h</td>
<td>15 days</td>
<td>90</td>
<td>44</td>
<td>19/6</td>
<td>11/12</td>
<td>7/6</td>
<td></td>
</tr>
<tr>
<td>Tavakkoli (2012) [30]</td>
<td>Iran</td>
<td>52</td>
<td>NE/MID + OCT</td>
<td>2.6 ± 0.7/2.6 ± 0.8</td>
<td>32.90 ± 6.0/34.5 ± 5.68</td>
<td>NE: 0.1–0.7 μg/kg/min/MID: 100–200 μg 3 times daily/OCT: 5–15 mg 3 times daily</td>
<td>15 days</td>
<td>90</td>
<td>15</td>
<td>5/6</td>
<td>4/4</td>
<td>0/0</td>
<td></td>
</tr>
</tbody>
</table>

TP: Terlipressin; OBS: observation; NE: norepinephrine; MID: midodrine; OCT: octreotide; HRS: hepatorenal syndrome; NR: not reported.
result, terlipressin was considered as the most effective in reversal of HRS and reducing the risk of MOLT but was associated with an increased AEs profile. Although norepinephrine provided less renal function and further survival benefit than terlipressin, it showed a safer AEs effect profile than other vasoconstrictors. However, in the absence of head-to-head comparisons, midodrine plus octreotide did not perform well in our analysis. It was associated with the lowest incidence of adverse events.

Figure 1. Network of the comparisons for primary and secondary outcomes of vasoconstrictor therapies in patients with type 1 HRS. The numbers along the link lines indicate the number of trials or pairs of trial arms. Lines connect the interventions that have been studied in head-to-head (direct) comparisons in the eligible randomized controlled trials. The width of the lines represents the cumulative number of trials for each comparison and the size of every node is proportional to the number of enrolled participants (sample size). HRS: hepatorenal syndromes; TP: terlipressin; OBS: observation; NE: norepinephrine; MID+OCT: midodrine plus octreotide.

Figure 2. Summary forest plot matrix of vasoconstrictor therapy for type 1 hepatorenal syndrome. Along the diagonals, the vasoconstrictor drugs included in the network meta-analysis were ranked with surface under the cumulative ranking probability. The best intervention was placed at the top of the graph. On both sides of the diagonal, summary forest plots and odds ratios with 95% confidence intervals for all possible combinations of the intervention pairs analyzed in the network analysis – in black color – were displayed above the pairwise meta-analysis results – in gray color – to allow visual assessment of consistency between two analyses. Any summary results without a gray-colored plot or estimate suggested a comparison for which no head-to-head trials existed. The summary plot and its corresponding numerical estimates were presented as mirror image. The numerical estimate of between-study variance heterogeneity was reported below the table.
rate of reversal of HRS and the higher incidence of MOLT and AEs followed by observation. These results may help clinicians in the selection of vasoconstrictor drugs.

To ameliorate renal dysfunction and improve survival of patients while waiting for definitive treatment with liver transplantation, terlipressin is the most widely studied vasoconstrictor drug, especially for patients with HRS-1. However, most previous traditional meta-analysis included trials with limited population only compared the terlipressin alone or with albumin against no intervention or albumin in the treatment of both HRS-1 and type 2 HRS [5, 7, 9, 31–33]. In agreement with our findings, a traditional meta-analysis included only four RCTs found that terlipressin with albumin was effective in reserving HRS-1 and associated with an improvement in survival of patients.
of survival among patients with HRS-1 [9]. Another meta-analysis of RCTs, and case-control trials, irrespective of duration of terlipressin treatment or type of HRS in either arm, reported similar results for reversal of HRS with terlipressin therapy (ORs 8.09, 95% CIs 3.5–18.6) but no clear survival effect [32]. Accordingly, a short-term survival advantage at 15 days (RR, 0.74, 95% CIs 0.37–0.97) in patients with HRS-1 treated with terlipressin was demonstrated in subgroup analyses by a previous pairwise meta-analysis that included a small number of patients [33]. Similarly, a trend that terlipressin reduced the incidence of MOLT in patients with HRS-1 was also reported in our study. All in all, the results of our analysis on the efficacy of terlipressin are remarkably similar with previous studies.

In addition to terlipressin, few observational trials or meta-analyses were published to compare the efficacy and safety of other vasoconstrictor drugs including norepinephrine and midodrine plus octreotide for patients with HRS-1 exclusively. Only one traditional pairwise meta-analysis published in 2014 evaluated relative effect and safety of norepinephrine compared to terlipressin in the management of HRS with a limited sample size of 154 patients, which found no difference in the reversal of HRS or mortality at 30 days between norepinephrine and terlipressin, but a decreased risk of AEs with norepinephrine (RR 0.36, 95% CIs 0.15–0.83) [34]. These findings are consistent with our results. However, it is problematic to analyze data from patients with HRS-1 and type 2 HRS since these two classifications have different diagnostic criteria and different responses to vasoconstrictors. The study using midodrine in patients with HRS-1 is more limited. Due to the lack of evidence from head-to-head RCTs which systematically compare effects of norepinephrine and midodrine, the number of patients on norepinephrine or midodrine in our analysis is too small to rank these treatments convincingly. Therefore, large clinical trials with multiple arms are urgently needed to resolve this issue. Finally, while the duration, dose, and mode of administration for the different vasoconstrictors have been the primary focus for treatment of HRS-1 patients, albumin is recognized as an integral part of the treatment paradigm and optimization of the albumin regimen could also potentially lead to improved response and survival. However, this study has shown that the effect of albumin alone (observation) was the most ineffective treatment. Unlike the vasoconstrictors, AEs attributable to albumin infusion have been reported only very infrequently in the included and other studies [35].

The new diagnostic HRS criteria in cirrhosis include cirrhosis with ascites, serum creatinine >1.5 mg/dl (133 μmol/l) after at least 2 days with diuretic withdrawal and volume expansion with albumin, absence of shock or parenchymal kidney disease, and no recent treatment with nephrotoxic drugs [20]. The revised diagnostic criteria of HRS abandoned exclusion of patients with infections and the use of minor criteria. HRS-1 is now characterized by rapid progressive renal failure with doubling of the initial serum creatinine increasing to 2.5 mg/dl (226 μmol/l) in less than 2 weeks. In our analysis, four studies classified patients using the previous vision of the international ascites club criteria [1,10,21,26,28]. The remaining trials used current diagnostic criteria. Additionally, there are many patients who are diagnosed with HRS-1 who present with infrarenal lesions. However, all trials in our analysis have similar baseline serum creatinine and MELD score for the treatment and control group, although whether the treatment effect is related to the criteria remains to be established (Table 1).

Our network meta-analysis has several strengths. First, it is worth mentioning that our network meta-analysis is the first Bayesian network meta-analysis which provides conclusive and complete pictures for propensity of the most widely used and most comprehensive vasoconstrictor therapies with respect to efficacy and safety outcomes among patients with HRS-1. Second, according to our extensive and rigorous literature search, we are confident that all eligible RCTs have been identified. Third, our study provides comprehensive figures of the combination of traditional forest plots and forest matrix to clearly present the results. Compared with cumbersome traditional forest plots which display the individual study effects together with the summary estimates, summary forest plot matrices presented in our study display the summary estimates from pairwise analysis alongside the network meta-analysis results to allow clinicians to directly assess the consistency between two analyses. Beyond that, these advanced plots not only enable easy comparison of pairwise and network meta-analyses results but also assist to provide a comprehensive presentation of important results (e.g. SUCRA probability) displayed on a single plot. In addition, we provided a formal rank order using SUCRA probability for all vasoconstrictor drugs by their capacity to improve the incidence of reversal of HRS and reduce the risk of MOLT or AEs by conducting a network meta-analysis, which was only attainable by a Bayesian approach. Finally, we performed an inconsistency diagnostic analysis by node-splitting method for all loops to decrease concerns regarding potential inconsistency.

However, the strengths of this network meta-analysis should be weighed against some limitations. First, due to the low number of head-to-head clinical trials comparing other vasoconstrictor
agents except for terlipressin, the study size assigned to different comparisons on norepinephrine or midodrine plus octreotide was too small in some studies we included which may affect the validity of our results. It should be noted that, to date, there is only one study which has included a combination of midodrine plus octreotide and terlipressin. Therefore, the SUCRA probability is challenging to interpret, affected by various factors, such as unbalanced number of trials per comparison in the network, limited number of studies, and insignificant effect sizes between treatments, and do not always imply a clinically important difference. It is possible that SUCRA probability for midodrine plus octreotide (which have the fewest number of trials) may be underestimated, whereas the SUCRA probability for terlipressin (which have the highest number of studies) may be biased upward. However, our study has established the most comprehensive vasoconstrictor treatment sample size for trials performed to date in the world in the treatment of HRS-1. Second, statistical heterogeneity of patients’ characteristics, such as patient populations, diagnosis of HRS, baseline serum creatinine, MELD score, duration of vasoconstrictor treatment, follow-up, the use of albumin, and the high risk of bias also may limit the strength of our conclusions. While only one of the pairwise meta-analyses includes enough RCTs to consider subgroup analyses, it is difficult to explore the source of heterogeneity. However, the results of statistical heterogeneity tests suggested a moderate ranking, which we believe is acceptable to the field of study today. Additionally, no substantial inconsistency was found in the network meta-analysis. Third, the quality of the included studies varied greatly. Randomization was adequate in all trials. However, information regarding allocation concealment and blinding were not adequately reported in most trials included in our analysis (Supplementary Figure 2), which might undermine the validity of overall findings. Although there is an absence of high-quality RCTs evaluating the benefit/risk profile of different vasoconstrictor drugs, we believe that performing a high-quality network meta-analysis of the existing literature is a valuable contribution to the field and to draw conclusions which may inform on the best interventional strategy. In addition, the paucity of information in terms of quality assessment has been commonly found in other systematic reviews and most studies included in this study were very similar in terms of design and conduct. In light of the limitations discussed above, these results should be interpreted alongside a certain relative treatment between comparisons such as HRS and should be used as guides for physicians and not as definitive values. Despite these limitations, this network meta-analysis provides the largest scale comparative information on the major clinical outcome profiles of different vasoconstrictor therapies in current use.

In conclusion, this study presents a concise and useful summary which describes apparent superior efficacy of terlipressin therapy in renal and survival benefits for patients with HRS-1; however, this may be offset by an associated increase in AEs. The analysis also provides evidence that norepinephrine may be an efficient and potentially safer alternative to terlipressin as it appears to be associated with less AEs. Our current analysis may provide new insights into treatment choice with valuable implications for patient care and future research. However, there remains a need for long-term, well-designed RCTs to study more vasoconstrictor drugs over longer period in the treatment of patients with HRS-1.

5. Expert commentary

HRS-1 is characterized by a progressive and rapid deterioration of renal function, usually accompanied by multiorgan failure. Compared with type 2 HRS, HRS-1 is more severe with a doubling of the initial serum creatinine level greater than 2.5 mg/dl along with decreased urine output, occurring rapidly and less than 2 weeks with typical features suggestive of multiorgan dysfunction. Up to now, most previous traditional meta-analysis included trials with limited population only compared the terlipressin alone or with albumin against no intervention or albumin in the treatment of both HRS-1 and type 2 HRS. However, since different HRS types have different diagnosis and different responses to vasoconstrictors, it may be questionable to combine data from patients with HRS-1 and type2 HRS in most previous meta-analyses. Moreover, several previous traditional meta-analyses confirmed that the use of terlipressin in conjunction with albumin was effective in reserving HRS-1 and associated with an improvement of survival among patients with HRS-1 [9]. A subsequent Cochrane meta-analysis presented that the initial RCTs included on evaluating the efficacy of terlipressin used crossover designs and were small sample size with a short treatment duration [10,11]. Although some clinical trials were able to demonstrate the efficacy of vasoconstrictor drugs with albumin than albumin only for HRS-1 patients, the comparative efficacy and safety of drugs is largely unknown as evaluated by traditional meta-analysis, with a lack of evidence from head-to-head clinical trials comparing the relative benefit and risk associated with use of these vasoconstrictor drugs. Thus, performing a high-quality network meta-analysis of the existing literature is the correct way to weigh the known data and decide on the best strategy.

6. Five-year view

Due to a lack of evidence from head-to-head clinical trials comparing the relative benefit and risk associated with use of these vasoconstrictor drugs, further large-scale, well-designed RCTs on this topic are still urgently needed. Additionally, further meta-analysis or network meta-analysis should establish subgroups to divide HRS-1 or type 2 HRS and differentiate AEs into major and minor or more specific.

Key issues

- Without treatment, the prognosis of HRS-1 is poor, with a mortality as high as 83% within 3 months and a median survival of only 2 weeks.
- With the lack of evidence from head-to-head clinical trials, the comparative efficacy and safety of vasoconstrictor therapies for treatment of patients with HRS-1 remain inconclusive.
Although some clinical trials were able to demonstrate the efficacy of vasoconstrictor drugs with albumin than albumin only for HRS-1 patients, the comparative efficacy and safety of drugs is largely unknown as evaluated by traditional meta-analysis.

Since different HRS types have different diagnosis and different responses to vasoconstrictors, it may be questionable to combine data from patients with type 1 and type 2 HRS in most previous meta-analyses.

Our network meta-analysis is the first Bayesian network meta-analysis which provides conclusive and complete pictures for propensity of the most widely used and most comprehensive vasoconstrictor therapies with respect to efficacy and safety outcomes among patents with HRS-1.

Our study provides comprehensive figures of the combination of traditional forest plots and forest matrix to clearly present the results.

Our study provided a formal rank order using SUCRA probability for all vasoconstrictor drugs by their capacity to improve the incidence of reversal of HRS and reduce the risk of MOLT or AEs by conducting a network meta-analysis, which was only attainable by a Bayesian approach.

Funding
This work was supported by grants from National Natural Science Foundation of China (81500665) Scientific Research Foundation of Wenzhou Y20160223, High Level Creative Talents from Department of Public Health in Zhejiang Province, and Project of New Century 551 Talent Nurturing in Wenzhou. This work was a part of PERSONS study.

Declaration of interest
The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

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Papers of special note have been highlighted as either of interest (●) or of considerable interest (▲) to readers.


This study was reported according to the preferred reporting items of systematic reviews and meta-analysis (PRISMA) statement.


The findings that norepinephrine was associated with less adverse events compared with other drugs are consistent with our results.