

Noradrenaline vs Terlipressin for Hepatorenal Syndrome (No To Hepatorenal Syndrome): A Meta-Analysis

Farrah Haidee Lynne P. Pedracio, M.D.*; Kenneth G. Samala, M.D.*; Jezreel L. Taquiso, M.D.*; Janus P. Ong, M.D.**

Abstract

Introduction: Hepatorenal syndrome (HRS) is a functional renal impairment associated with advanced cirrhosis. The best treatment is liver transplantation; however, many patients die before this can be done. Terlipressin improves renal function in HRS, but recent studies have shown similar effects with the cheaper and more readily available norepinephrine. This review included randomized trials comparing noradrenaline to terlipressin for patients with type 1 HRS, as defined by the International Ascites Club.

Objective: To determine the safety and effectiveness of noradrenaline in the management of HRS in terms of 1) reducing mortality, 2) reversal and 3) occurrence of adverse events

Methodology: For this meta-analysis paper, the researchers utilized an electronic search of databases and manual scanning of reference lists were performed. Standardized eligibility assessment was performed independently by three reviewers. Review Manager 5.0.23 was used to calculate odds ratios (OR) with 95% confidence intervals (CIs) as well as I² values for inter-trial heterogeneity. Standardized eligibility assessment was performed

independently by three reviewers.

Results: Thirty-six articles were found after electronic and manual searching. Three were assessed for validity and included in the final analysis. The total number of patients across all trials was 95. Noradrenaline was found not to differ from terlipressin in terms of 15-day survival rate (OR 0.17; 95% CI: 0.01-2.66), reversal of HRS (OR 1.07; 95% CI: 0.47-2.44), and a post-hoc analysis on disease-free survival (OR 0.78; 95% CI: 0.34-1.79). Results of sensitivity analysis were consistent with the previous findings (15-day survival: OR=1.21 95% CI = 0.52-2.83; HRS reversal: OR= 1.33, 95% CI = 0.56-3.13; disease-free survival: 1.35, CI =0.56-3.25). Only transient adverse effects were noted with either drugs.

Conclusion: There is inconclusive evidence that noradrenaline and terlipressin are significantly different in the reversal of HRS and reduction of mortality. Larger trials on noradrenaline or a non-inferiority trial may be needed to establish the equivalence of noradrenaline with terlipressin.

Keywords: hepatorenal syndrome, noradrenaline, terlipressin

Introduction

In cirrhosis, the local release of potent vasodilators such as nitric oxide leads to arterial vasodilatation in the splanchnic vascular bed. Nitric oxide also renders the splanchnic circulation resistant to various vasopressors.¹ The reduced peripheral resistance leads to effective arterial underfilling, which in turn leads to compensatory renal arterial vasoconstriction resulting in the condition known as hepatorenal syndrome (HRS).² This condition occurs in up to 11% of patients with advanced cirrhosis and refractory ascites.³

HRS is diagnosed using the following criteria¹:

- 1) Cirrhosis with ascites
- 2) Serum creatinine >1.5 mg/dl (133 µmol/L)
- 3) Absence of shock
- 4) Absence of hypovolemia as defined by no sustained improvement of renal function (creatinine decreasing to <133 µmol/L) following at least two days of diuretic withdrawal (if on diuretics), and volume expansion with albumin at 1.0 g/kg/day up to a maximum of 100 g/day
- 5) Absence of current or recent treatment with nephrotoxic drugs
- 6) Absence of parenchymal renal disease (in turn defined by the following: a) proteinuria <0.5 g/day b) no microhaematuria (<50 red cells/high powered field), and c) normal renal ultrasonography

HRS is further classified into Type 1 and type 2 HRS. Type 1 HRS is associated with a rise in serum creatinine to 2.5 mg/dl within two weeks.¹ Without intervention, most patients die within this period.⁴ Type

*Department of Medicine, University of the Philippines-Philippine General Hospital

**Section of Gastroenterology, Department of Medicine, University of the Philippines-Philippine General Hospital

Corresponding Author: Kenneth G. Samala, MD, UP-PGH, Manila, Philippines
Email: kenn.samala@gmail.com

2 HRS, meanwhile, is associated with a gradual rise in serum creatinine to 1.5 mg/dL and a median survival of four to six months.^{1,4} Patients with Type 2 HRS can eventually develop Type 1 HRS.⁵

The best treatment for HRS is liver transplantation (LT). However, due to organ shortage and the short survival associated with HRS, many patients die before this can be done. Furthermore, studies have shown an increased mortality among transplant patients with HRS. Treating HRS prior to LT may therefore improve outcomes.⁶

Vasoconstrictor drugs were first used together with volume expanders like albumin to improve renal function in cirrhotic patients 35 years ago. The mechanism by which vasoconstrictors and albumin improve the glomerular filtration rate (GFR) in patients with HRS is incompletely understood. It is, however, postulated that increasing the central blood volume with vasopressors and plasma expanders leads to inhibition of the sympathetic nervous and renin-angiotensin systems, making renal blood flow and GFR more responsive to changes in blood pressure¹.

Several randomized controlled trials and meta-analyses have proven that terlipressin, a vasopressin analogue, improves renal function in HRS. Terlipressin, however, is not readily available and is relatively expensive. Recent studies have investigated the possibility of using noradrenaline as an alternative^{7,8,9,10} A recent meta-analysis done by Gluud et al. in 2010 suggested that noradrenaline and terlipressin may be comparable in terms of their effects on renal function and survival. However, the authors were unable to make treatment recommendations due to inadequate sample size. The availability of recent trials on the use of noradrenaline in HRS may now allow comparison between these two treatments.^{7,10}

The objective of this study was to determine the safety and effectiveness of noradrenaline in the management of Type 1 HRS in terms of 1) reversing the syndrome 2) reducing mortality and 3) the occurrence of adverse events.

Materials and Methods

Methods of analysis and inclusion criteria were specified in advance and documented in a protocol.

Type of studies

This review included randomized controlled trials comparing the effect of noradrenaline with terlipressin on the mortality rates of patients with Type 1 HRS. Studies that investigated only one of the two drugs, or studies that were done solely on Type 2 HRS were excluded.

Types of participants

Only participants with Type 1 HRS were included since it is the type that causes significant morbidity and mortality. The target population consisted of adults diagnosed with HRS according to the criteria set by the International Ascites Club: (1) a low glomerular filtration rate as assessed by serum creatinine level greater than 1.5 mg/dL; 2) absence of shock, fluid losses, or treatment with nephrotoxic drugs; (3) no sustained improvement of renal function after oral diuretic withdrawal and plasma volume expansion; and (4) proteinuria less than 500 mg/d and no ultrasonographic evidence of parenchymal renal disease or urinary tract obstruction.

Types of intervention

The interventions studied were noradrenaline, given as an intravenous infusion; and terlipressin, given in intravenous boluses, both in combination with albumin.

Types of outcome measures

The primary outcome measured was 15-day survival rate, while the secondary outcomes were reversal of HRS and occurrence of adverse events.

Extensive search was done on the following electronic databases: PubMed, the Cochrane Library, GoogleScholar and Clinicaltrials.gov. Manual searches were performed by scanning reference lists of articles and registers of ongoing trials. The authors used the following search terms to identify possible trials: vasoconstrictor, noradrenalin, terlipressin, HRS, randomized controlled trial, meta-analysis and clinical trials. The last date of search was September 8, 2012.

Eligibility assessment was performed independently in a standardized manner using predefined data fields (a data extraction form including study quality indicators such as randomization, allocation concealment, blinding, follow-up rate and use of intention to treat analysis) set by three reviewers. Disagreements among the reviewers were resolved by consensus.

Results were presented as the odds ratio (OR) with 95% confidence intervals (CIs). I^2 values were calculated as measures of inter-trial heterogeneity. The analyses were done with the aid of Review Manager 5.0.23.

Results

A total of 32 potentially eligible studies were initially identified using electronic search. Manual searching (included checking of similar articles in the references of available studies) yielded an additional four references. Of the 36 potential studies, 33 studies were excluded for not meeting the inclusion criteria. Three articles were assessed for validity, and included in the final analysis. No unpublished relevant studies were retrieved. (Figure 1)

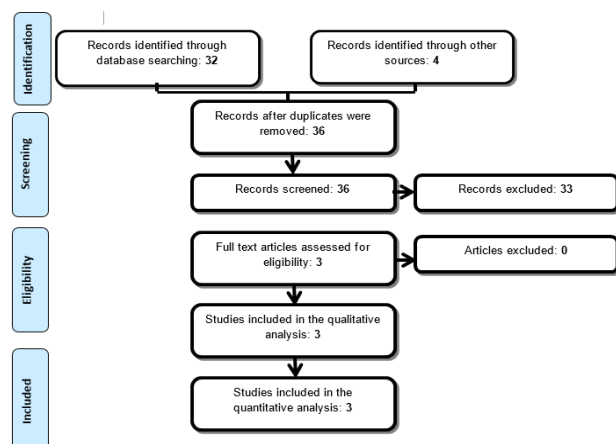


Figure 1: Flow of information through the different phases of the review.

Characteristics of Included Studies

Methods

All three studies finally selected for the review were randomized controlled trials published in English. The duration of follow up for both Singh and Sharma studies was 30 days and until death or liver transplantation for the study done by Alessandria. (Table I)

Outcomes

Primary

In all studies, primary outcome assessed reduction in mortality among patients on noradrenaline and terlipressin after 15 days of treatment.

Secondary

Reversal of HRS is defined as the decrease of 30% of serum creatinine level compared with the baseline value to a final value of 1.5 mg/dL (133 µmol/L) or lower during treatment. All studies evaluated adverse effects, including those of any kind and serious events. The timing of outcome measurement varied among the different studies but all of them included assessment at 15 days of treatment.

Table 2 shows the quality assessment of studies included in this review. Randomization and allocation concealment, but not blinding, were performed in all three trials. The authors deliberated and concluded that the absence of blinding (patients, health care providers and possibly data collectors) is acceptable for this kind of study since the administration of the two drugs was different (continuous infusion for noradrenaline; intravenous boluses for terlipressin), therefore blinding was not possible.

Moreover, since the outcome measures (reduction in mortality, improvement in serum creatinine from baseline) were objective and not affected by blinding, the authors accepted the lack of blinding in the included studies.

Table I: Summary of included studies evaluating the effectiveness of Noradrenaline versus Terlipressin for HRS

Source	Year	Type of Study	No. of Patients*	Inclusion Criteria	Intervention used	Dosage	Follow-Up
Singh, et. al	2012	RCT*	46	HRS as defined by the International Ascites Club	Noradrenaline and Terlipressin plus albumin infusion	Noradrenaline: 0.5 mg/hr infusion, titrated to effect Terlipressin: 0.5 mg every 6h, titrated to effect	30 days
Sharma, et.al	2008	RCT*	40	HRS as defined by the International Ascites Club	Noradrenaline and Terlipressin plus albumin infusion	Noradrenaline: 0.5 mg/hr infusion, titrated to effect Terlipressin: 0.5 mg every 6h, titrated to effect	30 days
Alessandria, et. al	2007	RCT*	22	HRS as defined by the International Ascites Club	Noradrenaline and Terlipressin plus albumin infusion	Noradrenaline 0.1 µg/kg/min, titrated to effect Terlipressin 1 mg every 4 h, titrated to effect	Until death or liver transplantation

*the total number of patients is originally 108, but since only Type 1 HRS is included in the criteria, the 13 were excluded because they are of the second type, making the total number of participants only 95

Table II: Quality measures of the randomized controlled trials used in this meta-analysis

Trials	Concealment of Randomization	RCT* stopped early	Patients Blinded	Health Care Providers Blinded	Data Collectors Blinded	Outcome Assessors Blinded
Singh, et. al	Yes	No	No	No	No mention	Yes
Sharma, et.al	Yes	No	No	No	No mention	Yes
Alessandria, et. al	Yes	No	No	No	No mention	Yes

Figure 2 shows the effect of noradrenaline on the 15-day survival rate of patients with HRS. This forest plot shows slight advantage of terlipressin over noradrenaline (OR=1.17, 95% confidence interval= 0.51, 2.66) however the advantage appears to be not statistically significant. The Chi2 value of 0.25 and the I2 value of 0% imply that the studies were homogenous, although the low I2 value may be due to the small number of studies included in this review.

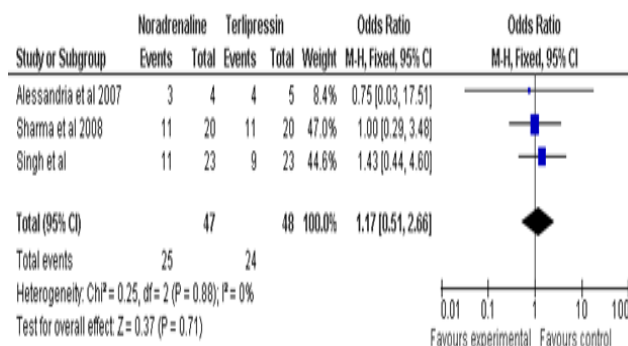


Figure 2: Forest plot of a fixed effects meta-analysis of randomized trials on noradrenaline versus terlipressin for HRS. The outcome measure is 15-day survival rate.

Figure 3 shows the effect of noradrenaline and terlipressin on HRS reversal. The forest plot shows a slight advantage of terlipressin over noradrenaline (OR= 1.07, 95% confidence interval = 0.47, 2.44); however, the advantage is again not statistically significant and the data is homogenous (Chi2 = 0.50 and I2 = 0%) as with the previous forest plot.

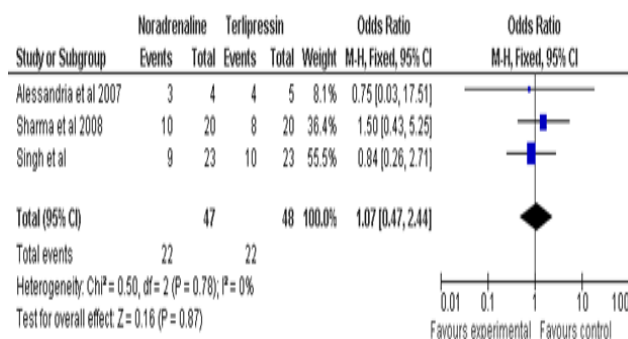


Figure 3: Forest plot of a fixed effects meta-analysis of randomized trials on noradrenaline versus terlipressin for HRS. The outcome measure is HRS reversal.

The authors noted that the studies also reported the proportion of surviving patients who also had HRS reversal. They then decided to do a post-hoc analysis on the effect of noradrenaline and terlipressin on disease-free survival, shown in the following forest plot (Figure 4). The analysis suggests a nonsignificant

advantage of terlipressin over noradrenaline (OR= 1.29, confidence interval=0.56, 3.01) and a homogenous data (Chi2 = 0.18 and I2 = 0%).

The reviewers noted the presence of a wide confidence interval for the study done by Alessandria et al. which is attributable to its small sample size and possibly from its slight difference from the two other studies in terms of doses of drugs used (Table 1). Therefore, a sensitivity analysis was done excluding the said study. Figures 5, 6 and 7 show the results of the sensitivity analysis done. Like the previous meta-analyses (Table 1), even when the outlier study was excluded, there is still a slight advantage of terlipressin over noradrenaline, but this advantage was not statistically significant (survival at 15 days: OR=1.21 95% confidence interval = 0.52, 2.83; HRS reversal: OR= 1.33, confidence interval = 0.56, 3.13; disease-free survival at 15 days: 1.35, confidence interval = 0.56-3.25). Data was homogenous for all three outcomes (survival at 15 days: Chi2 = 0.17 and I2 = 0%; HRS reversal: Chi2 = 0.07 and I2 = 0%; disease-free survival at 15 days: Chi2 = 0.05 and I2 = 0%).

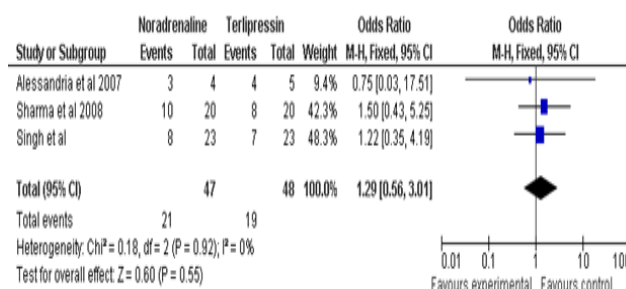


Figure 4: Forest plot of a fixed effects meta-analysis of randomized trials on noradrenaline versus terlipressin. The outcome measure is disease-free survival at 15 days.

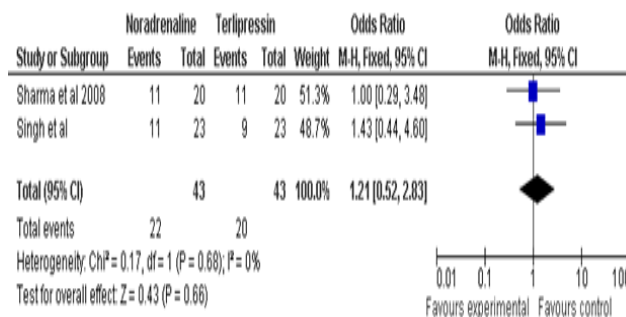


Figure 5: Forest plot of a fixed effects meta-analysis of randomized trials on noradrenaline versus terlipressin. The outcome measure is survival at 15 days.

Adverse events associated with terlipressin included the following: abdominal cramps, increased frequency

of stools, cyanosis of the toe and transient ventricular extrasystole. These adverse events were self-limiting. Meanwhile, the common adverse events reported by patients receiving noradrenaline is an atypical chest pain with normal electrocardiogram (ECG), troponin and creatine phosphokinase. Patients in both groups were noted to have asymptomatic ECG changes (ST segment depression of >0.1 mV on ECG, ventricular extrasystoles). All adverse events were transient.

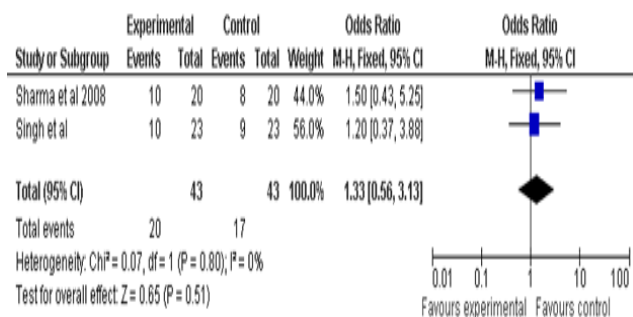


Figure 6: Forest plot of a fixed effects meta-analysis of randomized trials on noradrenaline versus terlipressin. The outcome measure is HRS Reversal

Discussion

Overall, the present review suggests that there is inconclusive evidence that noradrenaline and terlipressin are significantly different in terms of reducing mortality and reversing HRS. Although the present data shows the nonsignificant difference between the two interventions, we still cannot conclude that they are the same and that they may be used interchangeably. A more sophisticated and thorough non-inferiority analysis should be done in order to prove this. It is also worthwhile to note that both the initial analysis and subsequent sensitivity analysis done showed a wide confidence interval for all outcome measures. The authors believe that the small pooled sample size for this study was responsible for this and that the results may be imprecise.

The need for vasoconstrictors in the management of HRS has gained interest and popularity in recent years, probably owing to the fact that this condition is associated with very high mortality rates and that patients eventually die while awaiting liver transplantation. A meta-analysis done in 2014 compared different vasoconstrictors (including both noradrenaline and terlipressin among others) in the management of HRS. Among these agents, terlipressin was noted to be effective in prolonging the survival of patients and reversing HRS, with an added advantage of fewer side effects. Furthermore, the European Association for the Study of the Liver (EASL) released a clinical practice guideline citing

terlipressin as the recommended first line therapeutic agent for HRS (Level A1). Noradrenaline and other vasoconstrictor drugs (i.e., midodrine plus octreotide) were said to be potential alternative therapies (Level B1). This prompted the authors to investigate the use of noradrenaline for HRS since it is inexpensive and is readily available compared to terlipressin.

The review reported here combined data across three studies to approximate treatment effects with more precision than is possible in a single study. Fortunately, the studies included here are congruent in terms of patient population, intervention and outcome definitions. But as with any review, especially those concerning population of patients with uncommon diseases, a small sample size (n=95 for this review) can be considered as a limitation.

All the trials excluded patients with comorbidities such as coronary artery disease, sepsis, hepatocellular carcinoma, and diabetic nephropathy. One of the main concerns regarding the use of vasoconstrictor drugs are the presence of adverse events. These were mainly cardiovascular in nature, occurring in the form of ST segment depression⁹ and ischemic complications¹⁰. Gastrointestinal symptoms (abdominal cramps and watery diarrhea) were minor side effects reported in the terlipressin arms of all studies. Monitoring of patients on these medications should therefore include the use of electrocardiography to detect ischemia, regular inspection to detect limb ischemia or cyanosis and observation for any abdominal symptoms.

A probable next step for future trials is analysis using the Bayesian approach to definitively prove the non-inferiority of noradrenaline as compared to terlipressin. Since one of the limitations of this meta-analysis is the small sample size, the authors recommend more trials on larger patient populations. Lastly, since cost-effectiveness was not tackled in any of the trials included in this review, the authors suggest that a formal investigation regarding this aspect be undertaken.

Conclusion

There is inconclusive evidence that noradrenaline and terlipressin are significantly different in the reversal of HRS and reduction of mortality. Larger trials on noradrenaline or a non-inferiority trial may be needed to establish the equivalence of noradrenaline with terlipressin.

References

1. Salerno, F., Gerbes, A., Gines, P., Wong, F., and V. Arroyo. Diagnosis, Prevention and Treatment of Hepatorenal syndrome in cirrhosis. *Gut* 2007;56:1310-1318.
2. Glud, L., Christensen, K., Christensen E., and A. Krag. Systematic review of randomized trials on vasoconstrictor drugs for hepatorenal syndrome. *Hepatology* 2010;51:576-584
3. Adebayo, D., Morabito, V., Davenport, A., and R. Jalan.

- Renal dysfunction in cirrhosis is not just a vasomotor nephropathy. *Kidney International* 2015; 87: 509-515.
4. Gines P, Guevara M, Arroyo V et al. Hepatorenal syndrome. *Lancet* 2003; 362: 1819–1827.
 5. Arroyo, V., Gines, P., Gerbes, A.L., Dudley, F.J. et al. Definition and diagnostic criteria of refractory ascites and hepatorenal syndrome in cirrhosis. *Hepatology*. 1996; 23: 1641-1646.
 6. Fabrizi, F., Dixit, V., and P. Martin. Meta-analysis: Terlipressin therapy for the hepatorenal syndrome. *Aliment. Pharmacol. Ther.* 2006;24:935-944.
 7. Alessandria, C., Ottobrelli, A., Debernardi-Venon, W., Todros, L., Torrani, Cerenzia, M., Martini, S., Balzola F., Morgando, A., Rizetto M., and A. Marzano. Noradrenalin vs. Terlipressin in patients with hepatorenal syndrome: a prospective, randomized, unblinded pilot study. *Journal of Hepatology* 2007;47:499-505.
 8. Duvoux, C., Zanditenas, D., Hezode, C., Chauvat, A., Monin, J.L., Roudot-Thoraval, F., Mallat, A., and D. Dhumeaux. Effects of Noradrenaline and Albumin in Patients with Type I Hepatorenal Syndrome: A Pilot Study. *Hepatology* 2002;36:374-380.
 9. Sharma, P., Kumar A., Sharma, B. and S. Sarin. An Open Label, Pilot, Randomized Controlled Trial of Noradrenaline Versus Terlipressin in the Treatment of Type I Hepatorenal Syndrome and Predictors of Response. *American Journal of Gastroenterology* 2008;103:1689-1697.
 10. Singh, V., Ghosh, S., Singh, B., Kumar, P., Sharma, N., Bhalla, A., Sharma, A.K., Choudhary, N.S., Chawla, Y and C.K. Nain. Noradrenaline vs. terlipressin in the treatment of hepatorenal syndrome: A randomized study. *Journal of Hepatology* 2012;56:1293-1298.