JPSIM Journal of Pakistan Society of Internal Medicine

Original Article

Effectiveness of Noradrenaline and Albumin vs. Terlipressin and Albumin in Treating Hepatorenal Syndrome in Patients of Chronic Liver Disease

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Abstract

Objective: To compare the efficacy of noradrenaline and albumin versus terlipressin and albumin in the treatment of hepato-renal syndrome in patients with chronic liver disease.

Methods: This was a randomized controlled trial conducted from 2nd August 2022 to 1st February 2023 at the Department of Medicine & Gastroenterology, Medical unit III, Services Hospital Lahore. A total of 70 patients of age 18 to 70 years, both genders, diagnosed with chronic liver disease (CLD) having HRS were included. Patients with chronic kidney disease (CKD), history of ischemic heart disease, arrhythmias or cardiomyopathy were excluded. Group A received Inj. Terlipressin 1mg x 6 hourly along with Inj. Albumin 1 mg/kg on day 1 and then 20 mg/day. Group B received Nordrenaline initially 1 mg/hour along with Inj. Albumin 1 mg/kg on day 1 and then 20mg/day. Patients were followed for 48 hours. If there was decline of serum creatinine < 1.5 mg/dl within 48 hours, then efficacy was labeled.

Results: In our study, efficacy of noradrenaline and albumin was 80.0% versus 37.14% in terlipressin and albumin in treatment of hepato-renal syndrome in patients of CLD.

Conclusion: This study concluded that efficacy of noradrenaline and albumin is better than terlipressin and albumin in treatment of hepato-renal syndrome in patients of chronic liver disease.

Keywords: Liver cirrhosis, hepatorenal syndrome, nor-adrenaline.

How to cite this:

Malik H, Nadeem MA, Waheed A, Raza T. Effectiveness of Noradrenaline and Albumin vs. Terlipressin and Albumin in Treating Hepatorenal Syndrome in Patients of Chronic Liver Disease. J Pak Soc Intern Med. 2025;6(1): 26-31

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Received: 10-05-2024 **Revised:** 26-01-2025 **Accepted:** 22-02-2025

DOI: https://doi.org/10.70302/jpsim.v6i1.2506

Introduction

Liver cirrhosis is the end result of persistent and chronic hepatocellular injury. It is an irreversible pathological process featured by fibrosis and nodular regeneration.[1] The number of deaths due to this lethal disease is among the highest worldwide.[2] Around 8 million people live with HCV in Pakistan according to a National Hepatitis Survey. This ultimately leads to end stage liver disease, cirrhosis, and hepatocellular carcinoma (HCC).[3] The complications of cirrhosis e.g., hepatic encephalopathy, upper gastrointestinal bleed, Hepatorenal Syndrome (HRS) and hepatopulmonary syndrome, cause a high mortality rate of the disease.[4]

Hepatorenal syndrome is defined as the occurrence of renal failure in a patient with advanced liver disease in the absence of an identifiable cause of renal failure.[5] It is a severe and progressive functional renal failure in patients with chronic liver disease.[6] It also occurs in patients with acute fulminant hepatitis who have portal hypertension and ascites.[7] Mechanism for development of hepatorenal syndrome is still unclear. It includes renal vasoconstriction and arteriolar vasodilation in splanchnic system and reduced peripheral vascular resistance, while arterial vasodilation leads to a decrease in the effective blood volume, homeostatic activation of vaso-active systems and, consequently, renal vasoconstriction. Other pathogenetic mechanisms include increased endothelin concentration and adenosine level.[8]

Treatment of HRS includes the arterial vasoconstrictors, causing a vasoconstriction of the extremely dilated splanchnic vascular bed and increasing arterial pressure. The vasopressin analog terlipressin is the most widely

studied drug, especially in type 1 HRS.[9-10] However, it is expensive and unavailable in many countries. Patients with HRS should be treated by supportive measures (blood pressure support and antibiotics). Recently, trials using Terlipressin plus albumin and Octreotide plus Midodrine and Albumin combination have shown some improvement in renal function, but this regimen could only buy time for liver transplantation, which is the only standard treatment of HRS.[9] A number of comparative studies have reported almost a similar efficacy of noradrenaline and terlipressin i.e. 53% recovery in the case of noradrenaline and 57% recovery for the terlipressin group.[11] However, the comparatively cheaper price of noradrenaline makes it a better choice to use.

Goyal et al. conducted a comparative study on the effectiveness of noradrenaline and terlipressin on two groups of patients. HRS reversal was achieved in 47.6% cases of group A while that of 45% in group B.12 Gupta et al., found that noradrenaline with albumin were effective in 73% patients of hepato-renal syndrome, secondary to chronic liver disease.[13] Martin-Llahl et al., found that terlipressin with albumin were effective in 43% patients of hepato-renal syndrome, secondary to chronic liver disease.[14-15]

Rationale of this study was to compare the efficacy of noradrenaline and albumin versus terlipressin and albumin in the treatment of HRS in patients of chronic liver disease. Literature showed that combination of noradrenaline with albumin is more effective than the combination of terlipressin and albumin. However, data regarding efficacy of noradrenaline is still scanty with conflicting results and needs well-designed, randomized study to compare its efficacy with the present standard of care. Therefore, the aim of this study is to compare efficacy of noradrenaline plus albumin and terlipressin plus albumin in the treatment of hepato-renal syndrome in patients of chronic liver disease. This will help us to improve our practice and get updated evidence to be implemented in the local settings in the future.

Methods

It was a randomized controlled trial conducted at the Department of Medicine & Gastroenterology, Medical unit III, Services Hospital Lahore from 2nd August 2022 to 1st February 2023.

By using WHO calculator, sample size of 70 cases; 35 in each group as non-probability, consecutive sampling was calculated with 80% power of study, 5% significance level and percentage of efficacy i.e. 73% with noradrenaline with albumin[13] and 43% with terlipressin and albumin.[14]

Inclusion Criteria: Patients of age 18 to 70 years, both genders, diagnosed with chronic liver disease having Hepatorenal syndrome.

Exclusion Criteria: Patients with chronic renal dysfunction (serum creatinine > 1.2 mg/dl) and patients with a history of ischemic heart disease, arrhythmias or cardiomyopathy (on medical record).

After approval from ethical review board, 70 patients fulfilling the selection criteria were enrolled from wards. Informed consent was taken. Demographics like name, age, gender, body mass index (BMI), duration of chronic liver disease, hepatitis B or C, Child-Pugh class, diabetes (BSR>200 mg/dl), hypertension (BP≥ 140/90mmHg), duration of hepato-renal disease, were noted. Patients were randomized in two groups by random number table. Group A received Inj. Terlipressin 1mg x 6 hourly along with Inj. Albumin 1 mg/kg on day 1 and then 20 mg/day for 3 days. Dose was increased every 4 days in case of failure of serum creatinine to decline below 1.5 mg/dl. Maximum daily dose for terlipressin was 12 mg/day. Group B received Noradrenaline initially 1 mg/hour along with Inj. Albumin 1 mg/kg on day 1 and then 20mg/day for 3 days. Dose of noradrenaline was titrated to a maximum of 4 mg/hour in case of failure of serum creatinine to fall below 1.5 mg/dl.

Investigator following patients for response to treatment was blinded to group identity of patients. Patients were followed for 48 hours. If there was any decline in serum creatinine level < 1.5 mg/dl within 48 hours, then efficacy was labeled.

Data entry and analysis was done in SPSS 25. Shapiro-Wilk test was applied for normality of data. Quantitative variables e.g., age, BMI, duration of chronic liver disease, duration of hepato-renal disease, serum creatinine concentration before and after treatment were expressed as mean ± standard deviation. Qualitative variables e.g., gender, diabetes (BSR>200 mg/dl), hypertension (BP≥ 140/90mmHg), hepatitis B or C, Child-Pugh class, and efficacy were given as frequency and percentage. Both groups were compared for efficacy by using chi-square test. P-value ≤ 0.05 was taken as significant. Data was stratified for age, gender, BMI, duration of chronic liver disease, duration of hepato-renal disease, diabetes, hypertension, hepatitis B or C, Child-Pugh class. Post-stratification, both groups were compared for efficacy by using chi-square test in each stratum. P-value ≤ 0.05 was taken as significant.

Results

Age range in this study was from 20 to 70 years with the mean age of 41.33 ± 11.15 years. The mean age of patients in group A was 41.57 ± 10.65 years and in group B was 41.14 ± 11.63 years. Majority of the patients 47 (67.14%) were between 20 to 45 years of age as shown in table 1.

Table 1: *Distribution for both groups according to age, gender, duration (months and days) and Child Pugh Class (n=70).*

Age (years)	Group A (n=35)		Group B (n=35)		Total (n=70)	
	No. of patients	%age	No. of patients	%age	No. of patients	%age
18-45	23	65.71	24	68.57	47	67.14
36-70	12	34.29	11	31.43	23	32.86
Mean ± SD	**41.57 ± 10.65**		**41.14 ± 11.63**		**41.33 ± 11.15**	
Gender						
Male	22	62.86	21	60.0	43	61.43
Female	13	37.14	14	40.0	27	38.57
Duration (months)						
≤12	27	77.14	30	85.71	57	76.0
>12	08	22.86	05	14.29	13	24.0
Mean ± SD	**9.43 ± 3.28**		**8.77 ± 3.22**		**9.12 ± 3.24**	
Duration (days)						
≤7	24	68.57	20	57.14	44	62.86
>7	11	31.43	15	42.86	26	37.14
Child Pugh class						
A	17	48.57	18	51.43	35	50.0
B	15	42.86	12	34.29	27	38.57
C	03	8.57	05	14.29	08	11.43

Out of these 70 patients, 43 (61.43%) were male and 27 (38.57%) were females with male to female ratio of 1.6:1 (table 1). Mean duration of CLD was 9.12 ± 3.24 months (table 1).

Mean duration of HRS was 7.59 ± 3.12 years (table 1). Distribution of patients according to Child Pugh class is shown in table 1. Mean BMI was 29.34 ± 2.99 kg/m^2 (table 2). Distribution of patients according to DM, HTN and hepatitis is shown in table 2.

In our study, efficacy of noradrenaline and albumin (group B) was 80.0% versus 37.14% in terlipressin and albumin (group A) in treatment of hepato-renal syndrome in patients of chronic liver disease (figure 1). Stratification of efficacy with respect to age, gender, BMI, dura-

Table 2: *Distribution of patients according to BMI, Diabetes Mellitus, Hypertension and Hepatitis etiology (n=70).*

BMI (kg/m^2)	Group A (n=35)		Group B (n=35)		Total (n=70)	
	No. of patients	%age	No. of patients	%age	No. of patients	%age
≤30	21	60.0	19	59.38	40	57.14
>30	14	40.0	16	40.62	30	42.86
Mean ± SD	**29.26 ± 3.01**		**29.49 ± 2.99**		**29.34 ± 2.99**	
DM						
Yes	07	20.0	09	25.71	16	22.86
No	28	80.0	26	74.29	54	77.14
HTN						
Yes	10	28.57	11	31.43	21	30.0
No	25	71.43	24	68.57	49	70.0
Hepatitis						
B	13	37.14	14	40.0	27	38.57
C	22	62.86	21	60.0	43	61.43

tion of chronic liver disease, duration of hepato-renal disease, diabetes, hypertension, hepatitis B or C, Child-Pugh class is shown in table 3.

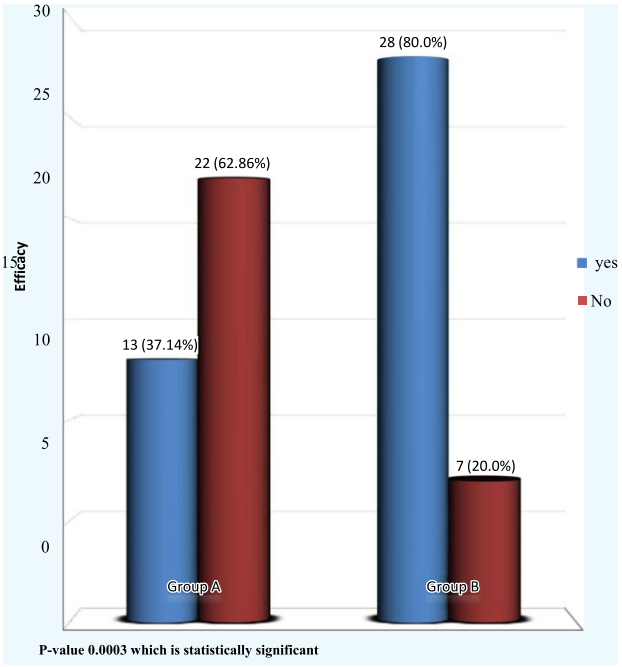

Figure 1: *Comparison of the efficacy of noradrenaline and albumin versus terlipressin and albumin in treatment of hepato-renal syndrome in patients of chronic liver disease.*

Discussion

Hepatorenal syndrome is a well-recognized complication of decompensated chronic liver disease. Most of the studies report approximately 8-10% per year incidence at one year and almost 40% at 5 year.[16] HRS significantly contributes to the morbidity and mortality of chronic liver disease as the average survival for HRS type 1 is one month and for type 2 is around 6 months.[16] HRS is generally considered a functional failure in the absence of known causes of acute kidney injury. Current guidelines recommend treatment with albumin and terlipressin; however studies have reported a beneficial role of noradrenaline as well.[17] Terlipressin is relatively expensive and its availability is a problem as compared to noradrenaline. Terlipressin is not FDA approved and it is not freely available in countries like Pakistan. Cost of treatment with noradrenaline is significantly low as compared to terlipressin. Few studies have compared role of these two drugs in HRS.

We had conducted this study to compare the efficacy

Table 3: *Stratification of efficacy with respect to age, gender, BMI, duration of chronic liver disease, duration of hepato-renal disease, diabetes, hypertension, hepatitis B or C, Child-Pugh class.*

		Group A (n=35)		Group B (n=35)		P-value
		Efficacy		Efficacy		
		Yes	No	Yes	No	
Age (years)	20-45	07(30.43%)	16 (69.57%)	19 (79.17%)	05 (20.83%)	0.0008
	46-70	06(50.0%)	06(50.0%)	09(81.82%)	02(18.18%)	0.109
Gender	Male	05(23.81%)	16(76.19%)	20(90.91%)	02(9.09%)	0.0001
	Female	08(57.14%)	06(42.86%)	08(61.54%)	05(38.46%)	0.816
Duration of CLD (months)	≤12	08(29.63%)	19(70.37%)	23(76.67%)	07(23.33%)	0.0004
	>12	05(62.50%)	03(37.50%)	05(100.0%)	00 (0.0%)	0.119
Duration of HRS (days)	≤7	09(37.50%)	15(62.50%)	16(80.0%)	04(20.0%)	0.005
	>7	04(44.44%)	05(55.56%)	12(80.0%)	03(20.0%)	0.074
Child Pugh class	A	06(33.33%)	12(66.67%)	14(82.35%)	03(17.65%)	0.003
	B	05(41.67%)	07(58.33%)	11(73.33%)	04(26.67%)	0.096
	C	02(40.0%)	03(60.0%)	03(100.0%)	00 (0.0%)	0.089
BMI (kg/m^2)	≤30	09(42.86%)	12(57.14%)	16(84.21%)	03(15.79%)	0.007
	>30	04(28.57%)	10(71.43%)	12(75.0%)	04(25.0%)	0.011
DM	Yes	02(28.57%)	05(71.43%)	05(55.56%)	04(44.44%)	0.280
	No	11(39.29%)	17(60.71%)	23(88.46%)	03(11.54%)	0.0002
HTN	Yes	03(30.0%)	07(70.0%)	08(72.73%)	03(27.27%)	0.050
	No	10(45.45%)	15(54.55%)	20(83.33%)	04(16.67%)	0.002
Hepatitis	**B**	05(38.46%)	08(61.54%)	12(85.71%)	02(14.29%)	0.011
	C	08(36.36%)	14(63.64%)	16(76.19%)	05(23.81%)	0.009

of noradrenaline and albumin versus terlipressin and albumin in treatment of hepato-renal syndrome in patients of chronic liver disease. In our study, efficacy of noradrenaline and albumin was 80.0% versus 37.14% in terlipressin and albumin in treatment of hepato-renal syndrome in patients of chronic liver disease. Goyal et al., conducted a comparative study on the effectiveness of noradrenaline and terlipressin on two groups of patients. HRS reversal was achieved in 47.6% cases of group A while that of 45% in group B.12 Gupta et al., found that noradrenaline with albumin were effective in 73% patients of hepato-renal syndrome, secondary to chronic liver disease.[13] Martin-Llahl et al., found that terlipressin with albumin were effective in 43% patients of hepato-renal syndrome, secondary to chronic liver disease.[14]

Various studies that compared the terlipressin and noradrenaline have reported a reversal of HRS in 39.1 to 73.9% with noradrenaline and 43.4 to 83% with Terlipressin. All the studies have described a reduction in serum creatinine, improved urine output and increased mean arterial pressure, serum sodium and urinary sodium, irrespective of treatment regimen. Most of the studies concluded that terlipressin was more expensive than noradrenaline.[18-21] Alessandria et al., in 2007 in a prospective study reported a success rate of 70% with noradrenaline and 83% with terlipressin.[18]

Sharma et al., in 2008 compared the noradrenaline and terlipressin in a randomized controlled trial and found 50% response with both drugs and similar survival rate in both groups. He also inferred that noradrenaline was cost effective as compared to terlipressin.[19] Singh et al., in 2012 achieved a 43.4% reversal with noradrenaline and 39.1% with terlipressin and a statistically significantly higher mortality with terlipressin.[20] Ghosh et al., in 2013 compared terlipressin and noradrenaline and observed a 73.9% reversal of HRS in both groups however; mortality was higher in noradrenaline group but it was not significant statistically. No significant adverse effects in any group. Treatment cost was lower with noradrenaline.[21]

Saif et al., in 2018 in a randomized controlled trial demonstrated a 53% response with noradrenaline and 57% with terlipressin and 100% survival at 30 day in both groups.[11] Sridharan et al., in 2018 analyzed 16 studies and mentioned that reversal of HRS was significantly better with noradrenaline and terlipressin. Cardiovascular side effects were higher with vasoactive drugs plus albumin than treatment with albumin alone. Mortality, incomplete HRS reversal, or side effects were similar for all interventions. He inferred that terlipressin was more effective in achieving complete HRS reversal.[22]

Mattos et al., in 2016 in his meta-analysis on four studies (154 patients) found a similar efficacy with terlipressin or noradrenaline for HRS reversal and similar rates of survival. However he found the strategy using terlipressin more economical under two different perspectives.[23] A meta-analysis by Gifford et al., in 2015 included 12 randomized clinical trials in his analysis and concluded that HRS reversal was higher with terlipressin and noradrenaline but the quality of evidence for noradrenaline was not convincing as the trials for noradrenaline were small and nonblinded. Terlipressin showed a reduction in mortality but the trials showing the mortality benefit had selection bias and terlipressin therapy was associated with higher incidence of adverse events.[10]

Our study has few limitations. First is the small sample size. This problem has been faced by most of the previous investigators also, as it is difficult to get a large number of patients with this morbid condition at a single centre. Most of the previously published studies could also enroll about 50 patients only. Secondly, plasma renin, urine sodium excretion and aldosterone levels were not measured in our study.

Conclusion

This study concluded that efficacy of noradrenaline and albumin is better than terlipressin and albumin in treatment of hepato-renal syndrome in patients of chronic liver disease. So, we recommend that noradrenaline and albumin should be used routinely in patients with hepato-renal syndrome, which will help in reducing the treatment cost as well as morbidity and mortality.

Ethical Approval: The IRB/EC approved this study via letter no.Ser. Hos/068 dated 11-03-2022.

Conflict of Interest: *None*

Funding Source: *None*

Authors' Contribution

HM: Conception
MAN: Design of the work
AW, TR: Data acquisition, analysis, or interpretation
HM, MAN: Draft the work
AW, TR: Review critically for important intellectual content
HM, MAN, AW, TR: Approve the version to be published
HM, MAN, AW, TR: Agree to be accountable for all aspects of the work

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