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Original Research Article

A prospective study to compare the efficacy of noradrenaline verses terlipressin in hepatorenal syndrome in patients with advanced cirrhosis

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ABSTRACT

Background: Hepatorenal syndrome (HRS) is functional renal failure occurring in advanced stage liver disease associated with poor prognosis. The best treatment is liver transplantation. Terlipressin is effective in treatment of HRS but noradrenaline has been suggested as cheaper and readily available alternative and we aimed to compare the efficacy of noradrenaline and terlipressin in patients with HRS.
Methods: 30 patients were allocated to each group and group A received infusion of noradrenaline at dose of 0.5 mg/hr (maximum 3 mg/hr) and group B received terlipressin at dose 1 mg intravenously 6 hourly until reversal of HRS or completion of 7 days of therapy. Intravenous albumin (20 g/day) was given to both groups. Decrease in serum creatinine and increase in daily urine output and mean arterial pressure (MAP) helped us in comparison.
Results: Out of 60 cirrhotics screened, 51 were randomised into group A (N=22) or group B (N=29). Baseline characteristics of both groups were similar. In group A, 0% showed complete response while 31.8% showed partial response but majority (68.2%) showed no response. In group B, 89.7% showed complete response and 6.9% showed partial response. Decrease in serum creatinine in both groups (group A- 3.91±1.58 mg/dl to 3.07±1.68 mg/dl; group B- 3.21±1.24 mg/dl to 1.36±0.87 mg/dl). Both groups showed an increase in MAP (group A- 76.93±6.18 mmHg to 89.49±6.93 mmHg; group B- 75.54±5.51 mmHg to 89.92±5.07 mmHg).
Conclusions: Noradrenaline was not as effective as terlipressin in treatment of HRS.

Keywords: Hepatorenal syndrome, Portal hypertension, Cirrhosis, Ascites, Vasoconstrictors

INTRODUCTION

Cirrhosis is characterized by fibrosis and formation of nodules in the liver parenchyma as a complication to chronic insult, leading on to alteration of normal lobular organization of the liver. Traditionally, it has been classified as compensated and decompensated cirrhosis and progression from compensated to decompensated state happens by account of development of 'Portal hypertension'. The occurrence of complications, namely variceal haemorrhage, ascites, spontaneous bacterial peritonitis, encephalopathy, hepatorenal syndrome or hepatopulmonary syndrome mark the onset of decompensated cirrhosis.[1] The Hepatorenal syndrome (HRS) is a form of functional renal failure without any histological renal pathology that occurs in about 10% of patients with advanced cirrhosis and is associated with very poor prognosis. The term 'Hepatorenal syndrome' was first coined by surgeons in the 1930's to describe renal failure occurring after biliary surgery or hepatic trauma in patients with previously normal renal function.

There are marked disturbances in the arterial renal circulation in patients with HRS and currently, the

'Arterial vasodilation theory' is the most widely accepted explanation for the circulatory dysfunction that occurs in patients with advanced cirrhosis. There is increased production or activity of vasodilators, mainly in the splanchnic circulation, with nitric oxide being the most important substance causing it and when the hepatic function starts to worsen, there is a progressive rise in cardiac output and a fall in systemic vascular resistance which occurs despite local increases in renal and femoral vascular resistance resulting partly from hypotension-induced activation of the renin angiotensin and partly by sympathetic nervous systems.[2] It has been shown that patients with advanced cirrhosis and bacterial translocation to mesenteric lymph nodes have increased production and release of proinflammatory cytokines [tumor necrosis factor alpha (TNF-a) and interleukin 6 (IL-6)] and vasoactive factors (nitric oxide- NO) in the splanchnic circulation, as well as increased serum levels of cytokines with reduction of sympathetic nervous system and increased cardiac output, as compared with patients without bacterial translocation.[3,4] In addition, markers of oxidative stress such as oxidized albumin has also been shown to increase in decompensated cirrhosis.[5,6] The decline in renal perfusion in this setting is associated with reduction in effective glomerular filtration rate (eGFR) and urinary sodium excretion per day (often to less than 10 meq/day) in patients with advanced cirrhosis, despite the intense renal vasoconstriction and a fall in mean arterial pressure.[2]

Current diagnostic criteria are based on an exclusion-based approach using serum creatinine as a biomarker. According to the latest 2015 position paper, HRS is diagnosed using the following revised criteria: (1) cirrhosis with ascites; (2) increase in serum creatinine >0.3 mg/dl or >50% or >1.5 times over baseline in 48 hours; (3) absence of shock; (4) absence of hypovolemia as defined by no sustained improvement of renal function following 2 days of diuretic withdrawal (if on diuretics) and volume expansion with albumin at a dose of 1 g/kg/day (maximum 100g/day); (5) absence of current or recent treatment with diuretics; and (6) absence of renal parenchymal disease as indicated by proteinuria >500 mg/day, microscopic hematuria (>50 RBC/high power field) and /or abnormal renal ultrasonography.[7]

There are 4 types of HRS: (a) HRS type 1 (Acute HRS)- progressive impairment in renal function and significant decrease in creatinine clearance within 1-2 weeks of presentation (doubling of initial serum creatinine to >2.5 mg/dl). There is multiorgan failure. Carries 80% mortality at 2 weeks; (b) HRS type 2 (chronic HRS)- reduction in GFR with rise in serum creatinine and refractory ascites, but is fairly stable, occurs gradually over weeks to months with serum creatinine of 1.5-2.5 mg/dl, usually associated with refractory ascites and has better prognosis than type 1; (c) HRS type 3: cirrhosis with types 1 or 2 HRS superimposed on chronic kidney disease or acute renal injury with median survival of 6 months; and (d) HRS type 4: fulminant liver failure with HRS.

The best treatment for HRS is liver transplantation.[8] However, due to organ shortage and the short survival associated with HRS, many patients die before this can be done. Therefore, bridge-to-transplantation solutions are required in such patients and treatment for HRS is required for the patients who are not candidates for liver transplantation. Theoretically, drugs that increase the blood pressure may be beneficial and hence, several vasoconstrictors have been evaluated for their effectiveness in this condition. The ideal pharmacological treatment for HRS would consist of a drug which has a selective vasodilatory action on the renal vessels but does not cause vasodilatation in other vascular beds, especially the splanchnic circulation. Terlipressin in combination with albumin has been studied as bridge to transplant therapy in type 2 HRS in patients awaiting or undergoing Liver transplantation (LT).[9] Midodrine, an orally administered α1-adrenergic agonist, and octreotide, a somatostatin analogue that inhibits endogenous vasodilators, have been used in combination with albumin for type 1 HRS.[10,11] A head-to-head randomized controlled study has been performed between terlipressin with albumin and midodrine plus octreotide and albumin. The group receiving terlipressin had a significantly higher rate of recovery of renal function in comparison to the group receiving midodrine and octreotide.[12] Norepinephrine (noradrenaline), a widely available IV-administered α1-adrenergic agonist, in combination with albumin, has been suggested as an alternative to the use of terlipressin but the studies are scarce.[13,14] So, the objective of our study is to determine the effectiveness of noradrenaline against terlipressin in management of HRS in patients with advanced cirrhosis in terms of reversing the syndrome.

METHODS

This hospital based, longitudinal comparative interventional study was carried out in Department of Medicine, Sri guru ram das charitable hospital attached to Sri Guru Ram Das Institute of Medical Sciences and Research, Sri Amritsar, Punjab during a period of March 2019 to August 2020. Cirrhosis was diagnosed based on clinical, biochemical, radiological means. HRS was diagnosed according to the standard criteria proposed by International Club of Ascitis: (1) cirrhosis with ascites; (2) increase in serum creatinine >0.3 mg/dl or >50% or 1.5 times over baseline in 48 hours; (3) absence of shock; (4) absence of hypovolemia as defined by no sustained improvement of renal function following 2 days of diuretic withdrawal (if on diuretics) and volume expansion with albumin at a dose of 1 g/kg/day (maximum 100 g/day); (5) absence of current or recent treatment with diuretics; and (6) absence of renal parenchymal disease as indicated by proteinuria >500 mg/day, microhematuria (>50 RBC/high power field) and /or abnormal renal ultrasonography.

Incusion criteria

Patients with following criteria were included- (1) patients presenting with advanced cirrhosis with HRS and age

between 18-80 years; and (2) patients who give consent for the study protocol by signing the informed consent.

Exclusion criteria

Patients with following criteria were excluded- (1) improvement in renal function after central blood volume expansion; (2) evidence of chronic kidney disease; (3) presence of severe sepsis, pancreatitis, or shock; (4) history of use of nephrotoxic drugs; (5) history of coronary artery disease, cardiomyopathy, ventricular arrhythmia, or obliterative arterial disease of the limbs; (6) patients undergoing renal replacement therapy; (7) patients with obstructive uropathy. Randomisation was carried out by dividing 60 patients into 2 groups (group A and group B) using stratified randomisation technique to receive treatment for 1 week.

Randomisation of participants into adrenaline and terlipressin groups was done using sequentially numbered, opaque sealed envelopes (SNOSE). Group A received continuous infusion of noradrenaline at an initial dose of 0.5 mg/hr via an automated infusion pump (maximum up to 3 mg/hr) aimed to achieve an increase in urine output of more than 100 ml in one day or increase in Mean arterial pressure (MAP) of up to 10 mm of Hg after being diagnosed with HRS. Group B received terlipressin at doses of 1 mg intravenously every 6 h until the serum creatinine level reduced to less than 1.5 mg/dl on two measurements 48 h apart. If even after 3 days the serum creatinine did not decline by at least 30% from baseline, the dose of terlipressin was increased to 2 mg every 6 h, with a cumulative maximum dose up to 12 mg/day. Patients in both the groups received daily IV albumin 20 g/day until the end of the study period. All patients had an indwelling urinary catheter for accurate measurement of urine output. Following formula was used for calculation of MAP:

$$MAP = DP + \frac{1}{3}(SBP - DBP) \; or \; MAP = DBP + \frac{1}{3}(PP)$$

Where DP is diastolic blood pressure, SP is systolic blood pressure and PP is pulse pressure.[15] Primary investigations done at the initiation of therapy were complete blood count, Prothrombin time index, liver function tests, renal function tests and serum electrolytes, Ascitic fluid studies, viral markers, ultrasonography, cultures.

Improvement in renal function was monitored in terms of increments in daily urine output and renal function tests were repeated every third day to see the improvement in serum creatinine. Response to treatment was defined as:

Complete response

Decrease in serum creatinine to a value of 1.5 mg/dl or lower during the treatment.

Partial response

Decrease of 50% or greater in the serum creatinine level compared with the baseline value to a final value higher than 1.5 mg/dl.

No response

Decrease of <50% as compared with baseline value or an increase in serum creatinine compared with the baseline value. The primary end point of the study was- complete response (i.e.; reversal of HRS); the secondary end points were- completion of 1 week of therapy or death. Data has been expressed as mean with standard deviation (SD) for quantitative variables. The results have been analysed at baseline and at the end of therapy. Comparisons between groups have been performed using Student's t-test and ANOVA test for quantitative variables and Chi square test for nominal/qualitative data. The baseline characteristics of all the patients have been compared in each treatment arm. A value of $p<0.05$ has been taken as significant.

RESULTS

As shown in Figure 1, 30 patients were allocated to each study group and received noradrenaline infusion+albumin (20 g/day) in group A and terlipressin boluses+albumin in group B according to aforementioned protocol until primary or secondary end points were achieved. While no patients were lost to follow up and in no patient therapy was discontinued due to side effects of the drugs, 8 patients died in group receiving noradrenaline, 5 of which died because of massive upper GI bleed and 3 died from ±upper UGI bleed. So, in our final study, 22 patients have been assessed in group receiving noradrenaline and 29 patients have been assessed in group receiving terlipressin. Baseline variables of each group have been shown in Table 1.

96.5% of patients in the terlipressin group but mere 31.8% in the noradrenaline group, in our study, responded to treatment. The response was also classified as complete and partial response based on fall of creatinine levels (complete response: decrease in serum creatinine to a value of 1.5 mg/dl or lower during the treatment. Partial response: decrease of 50% or greater in the serum creatinine level compared with the baseline value to a final value higher than 1.5 mg/dl). 89.7% patients were complete responders and 6.9% were partial responders in terlipressin group in our study, while 31.8% of patients in noradrenaline group showed only partial response in our study. Majority of patients (68.2%) in noradrenaline group showed no response (decrease of <50% as compared with baseline value or an increase in serum creatinine compared with the baseline value) while only 3.4% of patients in terlipressin group failed to respond to the treatment (Figure 2 and 3). In present study, noradrenaline group showed change in serum creatinine from 3.91±1.58 mg/dl to 3.07±1.68 mg/dl, p=0.007 and terlipressin group from 3.21±1.24 mg/dl to 1.36±0.87 mg/dl, p<0.001 (Table 2).

Our study showed a significant increase in MAP in both study groups (noradrenaline group- from 76.93±6.18 mmHg to 89.49±6.93 mmHg, p<0.001; terlipressin group from 75.54±5.51 mmHg to 89.92±5.07 mmHg, p<0.001) (Table 4). Both drugs increased the urine output in our study but change was more significant with terlipressin (noradrenaline group- from 493.41±240.42 ml/day to 781.27±342.57 ml/day, p=0.006; terlipressin group from 485.69±212.79 ml/day to 1346.21±544.64 ml/day, p<0.001) (Table 3).

Table 1: Baseline characteristics in two study groups.

Characteristics	Noradrenaline group (N=22)	Terlipressin group (N=29)	P value
Age (years)	54.64±15.60	53.45±13.01	0.143
Males (%)	72.7	82.8	0.388
Etiology (%)			
Alchohol	63.6	72.4	0.503
Hepatitis C	27.3	44.8	0.199
Others	18.2	3.4	0.080
Mean child pugh score	10.86±1.16	11.34±1.34	0.256
Mean MELD score	29.45±6.26	28.79±6.31	0.175
Mean serum bilirubin (mg/dl)	4.81±5.33	5.20±5.56	0.297
Mean serum albumin (g/dl)	2.15±0.62	2.12±0.50	0.041
Mean serum sodium (mmol/l)	133.76±6.98	134.17±6.05	0.201
Mean serum creatinine (mg/dl)	3.91±1.58	3.21±1.24	0.635
MAP (mm of Hg)	76.93±6.18	75.54±5.51	0.045

Note: Data was expressed as mean±standard deviation, MELD: Model for end stage liver disease, MAP: Mean arterial pressure.

Table 2: Mean change in serum creatinine (in mg/dl) in both study groups.

Groups	Serum creatinine			P value
	Baseline	**End of therapy**	**Change**	
Noradrenaline	3.91±1.58	3.07±1.68	0.84±0.28	0.007*
Terlipressin	3.211.24	1.36±0.87	1.85±0.21	<0.001*

Table 3: Mean change in urine output (in ml/day) in both study groups.

Groups	Urine output			P value
	Baseline	**End of therapy**	**Change**	
Noradrenaline	493.41±240.42	781.27±342.57	287.86±93.99	0.006
Terlipressin	485.69±212.79	1346.21±544.64	860.52±102.18	<0.001

Table 4: mean change in mean arterial pressure (map in mmHg) in both study groups.

Groups	Map			P value
	Baseline	**End of therapy**	**Change**	
Noradrenaline	76.93±6.18	89.49±6.93	12.55±1.32	<0.001
Terlipressin	75.54±5.51	89.92±5.07	14.37±0.95	<0.001

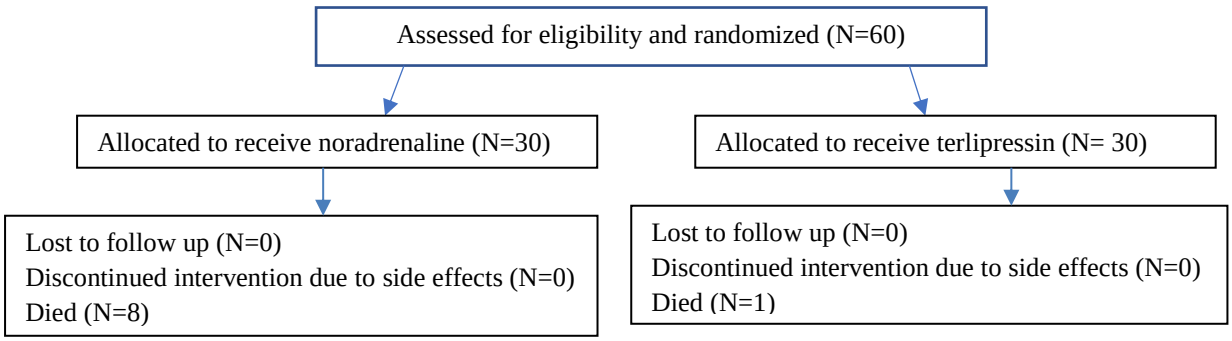

Figure 1: Showing flow of participants in both groups.

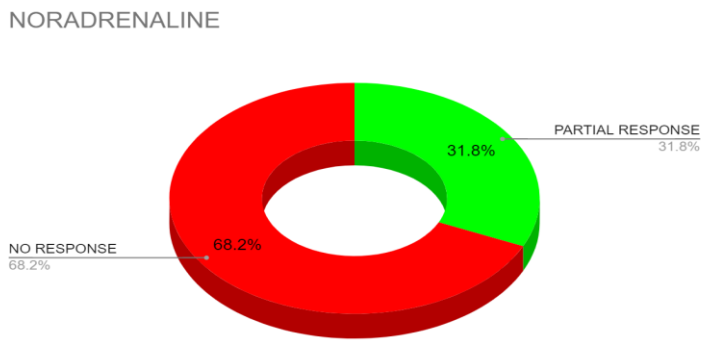

Figure 2: Response to therapy in noradrenaline group.

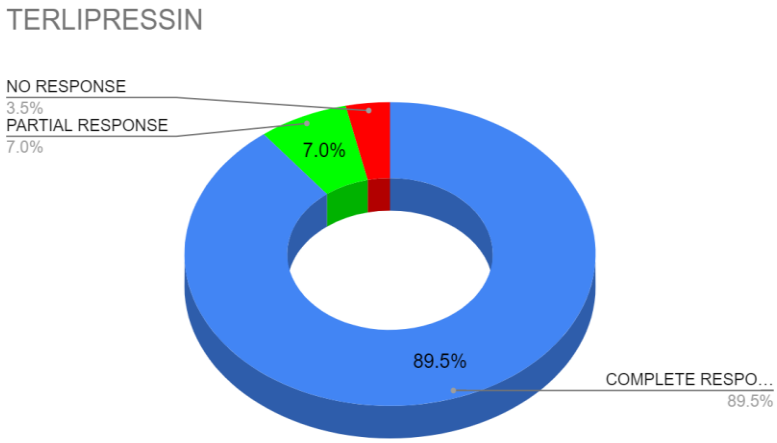

Figure 3: Response to therapy in terlipressin group.

DISCUSSION

The present longitudinal comparative interventional study was conducted in the setting of a tertiary care center with the aim of assessing the efficacy of noradrenaline versus terlipressin in HRS in patients with advanced cirrhosis using serum creatinine as the index biomarker for assessing the response to treatment. Our study is double blinded and is one of the few studies that directly compares the efficacy of these 2 drugs in treatment of patients with advanced cirrhosis with HRS. Most of the earlier studies were unblinded. [14,16,18] Our study was meant to assess the response in both HRS type 1 and type 2 like the pilot study but all the patients enrolled in our study were of HRS type 1 by a probability of chance.[14] Most of the studies done till now also compared the 2 drugs' response in HRS type 1.[16,17,19,20] The comparison of response rates has been shown in Table 5.

Table 5: Comparison of response rates of hrs with noradrenaline and terlipressin in various studies.

Study	N	HRS type	Noradrenaline (%)	Terlipreesin (%)
Alessandria et al[14]	22	HRS type 1 and HRS type 2	70	83
Badawy et al[21]	51	HRS type 1	40	46.15
Ghosh et al[22]	46	HRS type 2	73	73.9
Sharma et al[13]	40	HRS type 1	55	55
Singh et al[16]	46	HRS type 1	43.4	39.1
Goyal et al[17]	41	HRS type 1	47.6	45
Indrabi et al[18]	60	HRS type 1	53	57
Present study	51	HRS type 1	31.8	96.5

Our study demographics were similar to previous studies. Mean age of patients was 54.04 years in our study with male (78.4%) to female (21.6%) ratio of 3.6:1, just like in all other studies where mean age of patients lied in the age group of 40-60 years with male sex predominance. This could be due to the fact that males have higher incidence of developing cirrhosis following decades of alcohol consumption, which was found to be the most common etiology of cirrhosis in our patients similar to all previous studies. 68.6% of total patients analyzed (N=51) had history of chronic alcohol consumption, all of them being males in our study as no female patients gave any positive history. This could be due to the taboo surrounding alcohol consumption by females in India which is hence culturally prohibited in female population of India. The second common cause of cirrhosis in our study was hepatitis C virus (HCV) reactivity (37.3%) seen in both males and females. This was because HCV poses a significant health problem in the state of Punjab, India owing to the higher prevalence of risk factors like unsafe medical practices (including unsafe injections and dental procedures) and intravenous drug usage24. The results of our study have been tabulated in Table 2 to 4 while responses have been shown figuratively in Figure 2 and 3.

In our study, since both drugs showed unequal responses, no further analysis was possible for ascertaining other factors as having prognostic significance in predicting the outcome of treatment in both study groups between responders and non-responders. Although a cost-effectiveness analysis was not the main aim of this study, the cost of noradrenaline was found to be lower than terlipressin. However, terlipressin has some advantage over noradrenaline as it is given as an intravenous bolus through a peripheral vein, while noradrenaline is given intravenously as a continuous infusion preferably via a central venous catheter, usually in the setting of intensive care unit that nullifies the cost benefit gained from lesser cost of this drug. Mapping survival of patients post therapy was not the aim of this study.

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 enrol about 50 patients only. Secondly, plasma renin, urine sodium excretion and aldosterone levels were not measured in our study.

CONCLUSION

Our study suggests that noradrenaline might not be an attractive and equally efficacious alternative to use of terlipressin in HRS, as suggested by previous studies. Larger multi-centric clinical trials comparing noradrenaline with terlipressin in the treatment of HRS are required to draw firm conclusions on this subject.

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