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A study of the effect of terlipressin with albumin vs only albumin in patients diagnosed with hepatorenal syndrome (HRS)

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Abstract---Background: Hepatorenal syndrome (HRS) is a potentially reversible, functional renal failure that occurs in patients with advanced liver disease. HRS is generally characterized by increased serum creatinine, azotemia, reduced diuresis, increased urine osmolarity, and reduced urine sodium values without signs of organic kidney damage¹. AIM: The aim of the study is to investigate the efficacy, adverse effects, and outcomes of Terlipressin with Albumin vs. only Albumin in patients diagnosed with hepatorenal syndrome. Material and methods: A single centred hospital-based descriptive ,observational study was conducted in patients admitted with a diagnosis of hepatorenal syndrome for 18 months (October 2019 to March 2021). A total 80 cases were studied. Results: All the parameters including Total Bilirubin, SGPT (Serum glutamate pyruvate transaminase), INR (Internationalised normalised ratio) and Serum Albumin were found to be similar in both the groups

except except SGOT ($p=0.002$) which was found to be significantly lower in Terlipressin +Albumin treatment group (61.89 ± 47.83) compared to only albumin (96.80 ± 109.30). Those who were treated with Terlipressin +Albumin showed significant decrease in serum creatinine. A significant decrease in serum creatinine was observed at Day 5 (1.73 ± 1.49) from Day 1 (3.47 ± 1.68) making a mean percentage decrease of 50.14%. Whereas in the group receiving Albumin only a decrease of only 9.53% was obtained. Majority of the patients receiving Terlipressin +Albumin combination achieved complete response 60% whereas only 40% had no response. Those receiving Albumin alone, majority had no response 85% and only 15% had shown complete response to treatment. The comparison was found to be significant with (p) value of 0.000032. Conclusion: The administration of Terlipressin plus Albumin improves renal function in patients with HRS and that a reversal of hepatorenal syndrome is strongly associated with improved survival.

Keywords---cirrhosis, hepatorenal failure, terlipressin, albumin.

Introduction

Cirrhosis of liver is the tenth leading cause of death in India and a major cause of disease burden among the population. The expenditure in treatment not only burns out the country's economic resources but also a major cause of sickness absenteeism leading to man days losses. ^{1, 2} According to the latest WHO data published in May 2014 "Deaths due Liver Disease" and its complications in India is killing almost 216,865 people and accounts for nearly 2.44% of total deaths and India ranks 61 among the other world nations in mortality due to cirrhosis.

The disease course is further altered by the development of numerable complications like varices, hepatic encephalopathy, coagulopathy, hepatopulmonary syndrome, cirrhotic cardiomyopathy, hepatorenal syndrome that carries a poor prognosis. ³ Among the various complications the development of hepatorenal syndrome has a devastating course and outcome in cirrhotic patients. HRS is usually an extended spectrum of prerenal azotemia and therefore is potentially reversible. But after the evolution of the disease, the median survival is only 2 weeks without liver transplantation or management with vasoconstrictors. ⁴ HRS is a part of events occurring in the background of cirrhosis with acute liver injury.

Two important pathogenesis of HRS

- Splanchnic arterial vasodilatation
- Renal arterial vasoconstriction

This leads to progressive renal failure with normal kidneys in histological examination. ³ Usually HRS can be diagnosed only after the rise in blood urea nitrogen and serum creatinine. By then the disease has progressed so that it is no longer reversible and has a poor outcome. But the disease can be predicted in

advance by the estimation of renal resistive index that increases before a considerable period of time by Doppler ultrasound and so measures can be implemented to prevent the disease progression by avoiding the excess use of diuretics and nephrotoxic agents, avoiding large volume paracentesis etc. Renal dysfunction may be corrected by treating of portal hypertension, liver transplantation, transplantation of the kidneys into a noncirrhotic recipient, and medical management. ⁵

HRS is the consequence of a severe vasoconstriction of the renal circulation that causes a marked reduction in renal blood flow and glomerular filtration rate. ⁶ All attempts to induce renal vasodilatation by the administration of vasodilator drugs have been unsuccessful. ⁷ It is currently considered that HRS is the final consequence of a marked vasodilation of the splanchnic circulation secondary to an increased production of vasodilators in the splanchnic bed. As a result, the effective arterial blood volume is severely reduced, and there is compensatory activation of major vasoconstrictor systems, which are responsible for renal vasoconstriction. ^{8, 9} This pathogenic concept has modified the approach to therapy of HRS, and several studies have been reported assessing the efficacy of vasoconstrictors, particularly vasopressin analogues to improve effective arterial blood volume.¹⁰ These studies show that vasopressin analogues improve renal function in patients with HRS. However, the available information is limited because studies are either retrospective, have a small number of patients, or are not randomized. Therefore, the current study was undertaken to evaluate the effects of terlipressin on renal function and survival of patients with cirrhosis and HRS.

Aim and Objectives

Aim

To investigate the efficacy and outcome of terlipressin with albumin versus only albumin in patients diagnosed with hepatorenal syndrome .

Objectives

- To include patients diagnosed with HRS in the study.
- To study the clinical and biochemical profile of included patients
- Two groups were made with age and gender match, one group has received albumin and other group has received albumin with terlipressin.
- To compare the efficacies of both (terlipressin with albumin, albumin) drugs.

Materials and Methods

Study design. This was a cross-sectional, observational, descriptive study.

Study setting. This was a single centre hospital-based study, in patients who were admitted to the Intensive Care Unit (ICU).

Study duration. Present study was performed over a period of 18 months from October 2019to March 2021.

Inclusion criteria

Major Criteria

- i. Chronic or acute liver disease with advanced hepatic failure and portal hypertension.
- ii. Low GFR as indicated by serum creatinine > 1.5 mg/dL or 24 hr creatinine clearance < 40 mL/min.
- iii. Absence of shock, on-going bacterial infection, and current or recent treatment with nephrotoxic drugs and absence of gastrointestinal fluid losses (repeated vomiting or intense diarrhoea) .
- iv. No sustained improvement in renal function (decrease in serum creatinine \leq 1.5 mg/dL or increase in creatinine clearance to \geq 40 mL/min) following diuretic withdrawal for 48 hrs and expansion of plasma volume with 1.5 L of isotonic saline.
- v. No sonographic evidence of obstructive uropathy or parenchymal renal disease.

Additional Criteria

1. Serum sodium < 130 mEq/L.
2. Cirrhosis with ascites.
3. Serum creatinine > 133 μ mol/L (1.5 mg/dL).
4. No current or recent treatment with nephrotoxic drugs.

Exclusion criteria

The exclusion criteria were as follows:

Presence of severe extrahepatic condition, including cardiovascular (coronary and/or peripheral arterial disease) and neurological diseases, septic shock, and hepatocellular carcinoma.

Sample Size: A total of 80 patients diagnosed with Hepatorenal syndrome were studied

Two groups were made with age and gender match, one group has received albumin and other group has received albumin with Terlipressin

Grouping

- Albumin Group: n=40, Patients receiving only albumin
- Terlipressin + Albumin Group: n=40, Patients receiving both Terlipressin +Albumin

Statistical analysis

All the data analysis were performed using IBM SPSS (statistical package for social sciences) ver.20 software. Frequency distribution and cross tabulation were performed to prepare the tables. Results are presented as mean \pm standard deviation (SD) and median (minimum – maximum). Continuous variables were compared with Student's *t* test, and Mann–Whitney test. Categorical variables

were compared with Pearson Chi square and Fisher's exact tests. A $p' < 0.05$ was considered as statistically significant.

Results

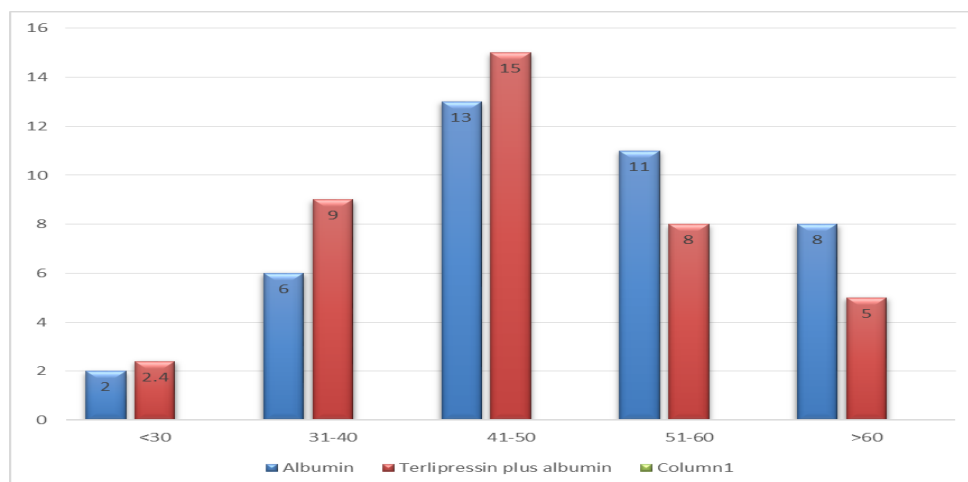
Demographic profile and frequency distribution of age in both the groups

In the present study 80 subjects were divided equally into two groups of 40 each. One group of patients have received Terlipressin and albumin, while the other group has received only albumin. The present study shows the age distribution between two regimens. No significant difference was obtained between the mean age and age distribution between two groups as revealed by the insignificant p value of 0.71. This confirms that the effect obtained in present study was not influenced by the age of the patients. (Table 1, Figure 1)

Table 1: Demographic profile and frequency distribution of age in both the groups

Age groups (years)	Treatment		Total	P value
	Albumin	Terlipressin +Albumin		
≤30	2	3	5	0.71
31-40	10	5	18	
41-50	13	15	23	
51-60	10	9	21	
>60	5	8	13	
Grand Total	40	40	80	
Mean age	51.04	46.94	49.25	0.742
SD	11.40	12.56	12.02	

Figure 1: Demographic profile and frequency distribution of age in both the groups



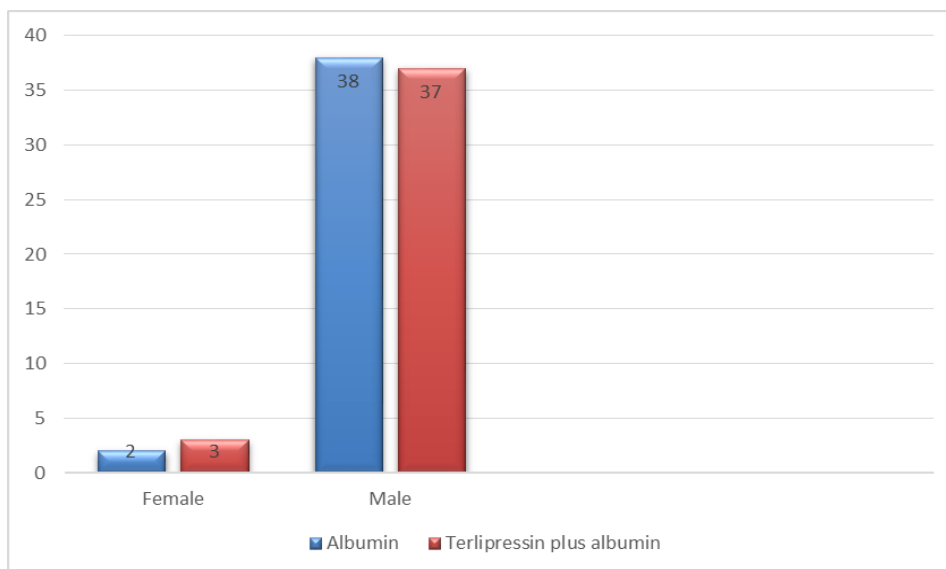
Demographic profile and frequency distribution of sex in both the groups

In the present study there was no significant difference observed between the sex distribution between the two drugs regimens as revealed by the insignificant p value of 0.44. This confirms that the effect of both drugs regimens obtained in present study is not influenced by the sex of the patient. (Table 2, Figure 2)

Table 2: Demographic profile and frequency distribution of sex in both the groups

Sex	Treatment		Total	P value
	Albumin	Terlipressin +Albumin		
Female	3	3	5	0.44
Male	37	38	75	
Grand Total	40	40	80	

Figure 2: Demographic profile and frequency distribution of sex in both the groups



Study of distribution of Etiology between the study groups

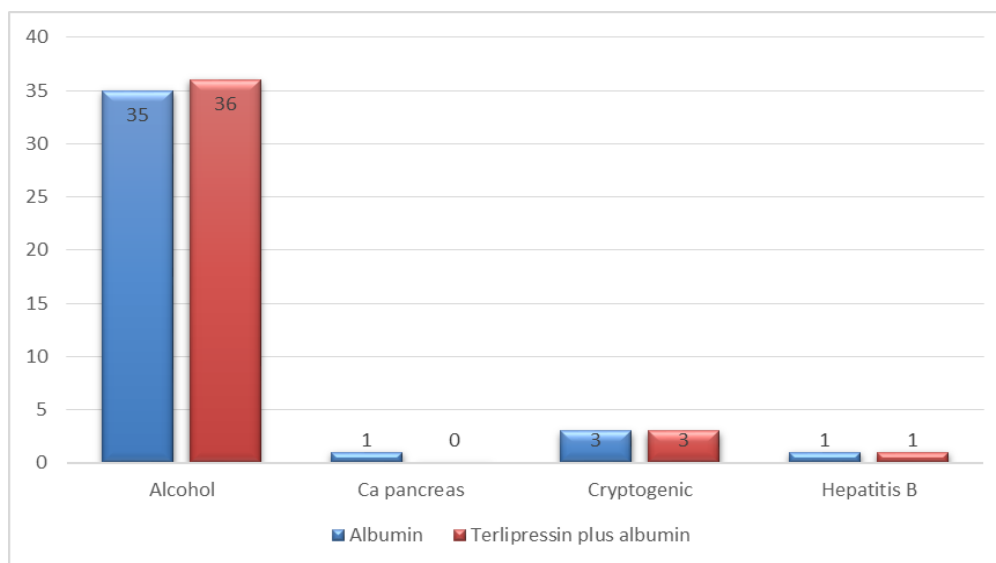
In this present study the most common etiology was alcohol (n=71). However, no significant difference was obtained in terms of distribution of etiology between the treatment as revealed by the insignificant p value of 0.79. (Table 3, Figure 3)

Table 3: Study of distribution of Etiology between the study group

Etiology	Treatment		Total	P value
	Albumin	Terlipressin +Albumin		
Alcohol	35	36	71	0.79
Ca pancreas	1	0	1	

Cryptogenic	3	3	6
Hepatitis B	1	1	2
Grand Total	40	40	80

Figure 3: Study of distribution of Etiology between two groups



Study of Comparison between LFT parameters between two groups

In the present study all the parameters including total Bilirubin, SGPT, INR and Sr.Albumin were found to be similar in both the groups except SGOT ($p=0.002$) which was found to be significantly lower in Terlipressin +Albumin treatment group (61.89 ± 47.83) compared to only albumin (96.80 ± 109.30). (Table 4, Figure 4,5,6,7,8)

Table 4: Study of Comparison between LFT parameters between two groups

Parameters	Treatment		Total	P value
	Albumin	Terlipressin +Albumin		
Total Bilirubin.	11.41±8.77	12.28±10.10	11.79±9.33	0.482
SGOT	96.80±109.30	61.89±47.83	81.53±89.12	0.002
SGPT	56.47±33.50	58.54±78.28	57.38±45.23	0.321
INR	2.34±0.51	2.59±0.67	2.45±0.59	0.631
Sr.Albumin	2.47±0.53	2.37±0.74	2.43±0.63	0.246

Figure 4: Total bilirubin

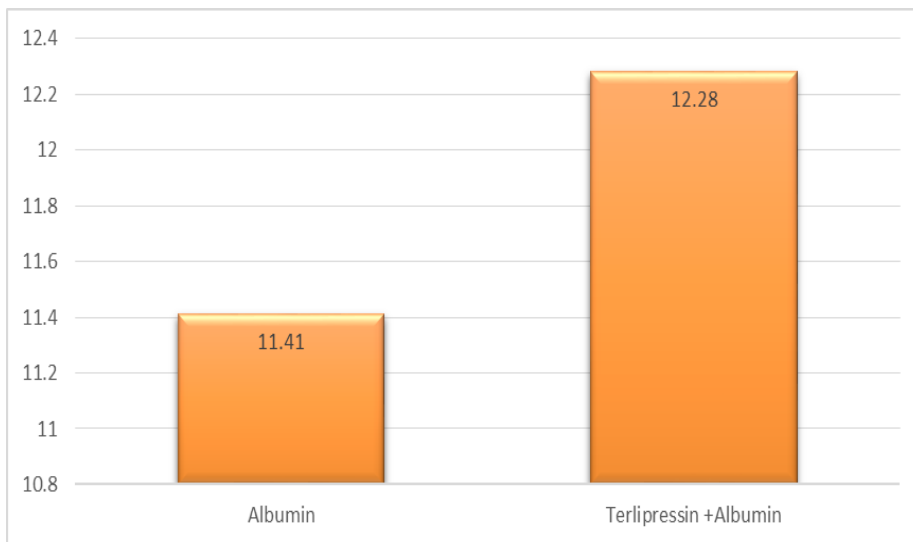


Figure 5 : Serum glutamate oxaloacetate transaminase

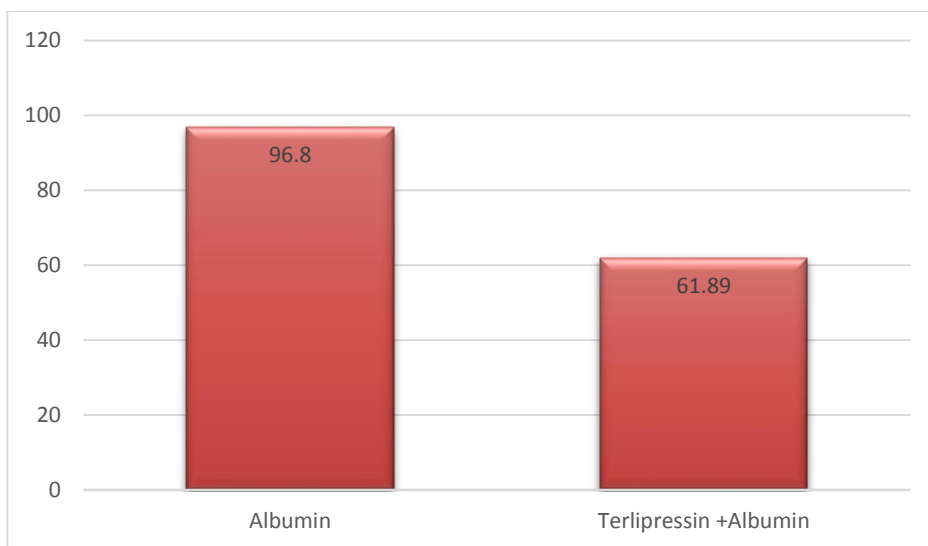


Figure 6: Serum glutamic pyruvate transaminase

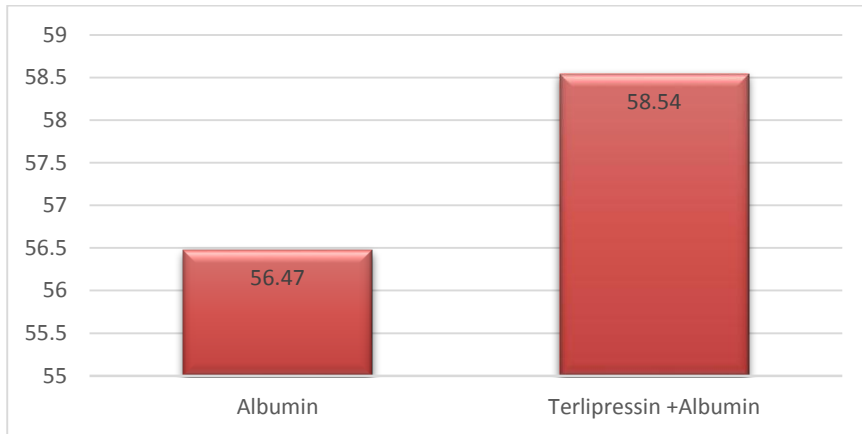


Figure 7: International normalised ratio

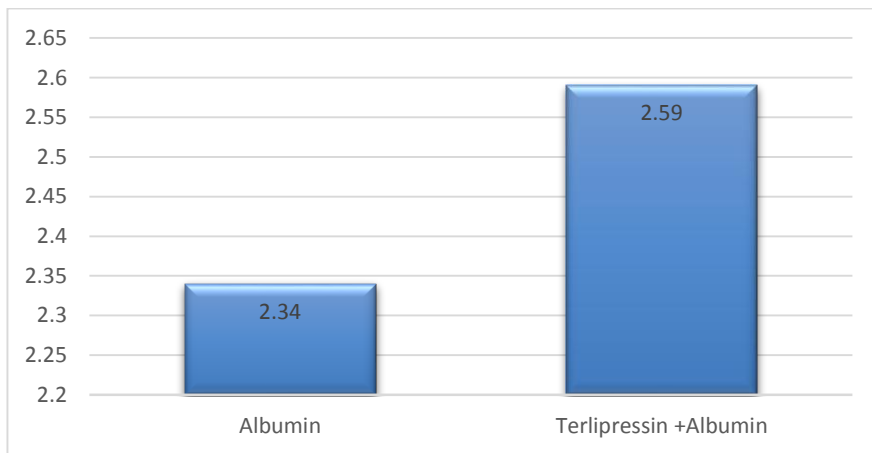
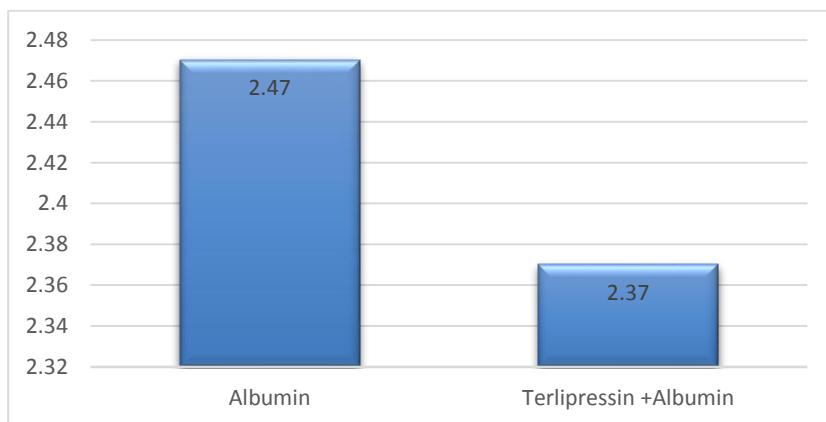


Figure 8: Serum albumin



Study of Comparison between serum creatinine levels in both the groups

In the present study those who were treated with Terlipressin +Albumin showed significant decrease in serum creatinine. A significant decrease in serum creatinine was observed on Day 5 (1.73 ± 1.49) from Day 1 (3.47 ± 1.68) making a percentage decrease of 50.14%. Whereas in the group receiving albumin only a decrease of 9.53% was obtained. Moreover, the decrease in serum creatinine in albumin group was insignificant with p value of 0.237. (Table 5, Figure 9,10)

Table 5: Study of Comparison between serum creatinine levels in both the groups

Timeline	Treatment		Total	P value
	Albumin	Terlipressin +Albumin		
Day 1	3.88 ± 2.46	3.47 ± 1.68	3.70 ± 2.15	0.582
Day 2	3.52 ± 2.17	2.93 ± 1.37	3.25 ± 1.87	0.024
Day 3	3.57 ± 2.49	2.44 ± 1.30	3.08 ± 2.12	0.031
Day 4	3.61 ± 2.55	2.12 ± 1.51	2.96 ± 2.27	0.023
Day 5	3.51 ± 2.41	1.73 ± 1.49	2.73 ± 2.23	0.001
% Decrease from Day 1	9.53	50.14		
P value	0.237	<0.001		

Figure 9: Comparing serum creatinine

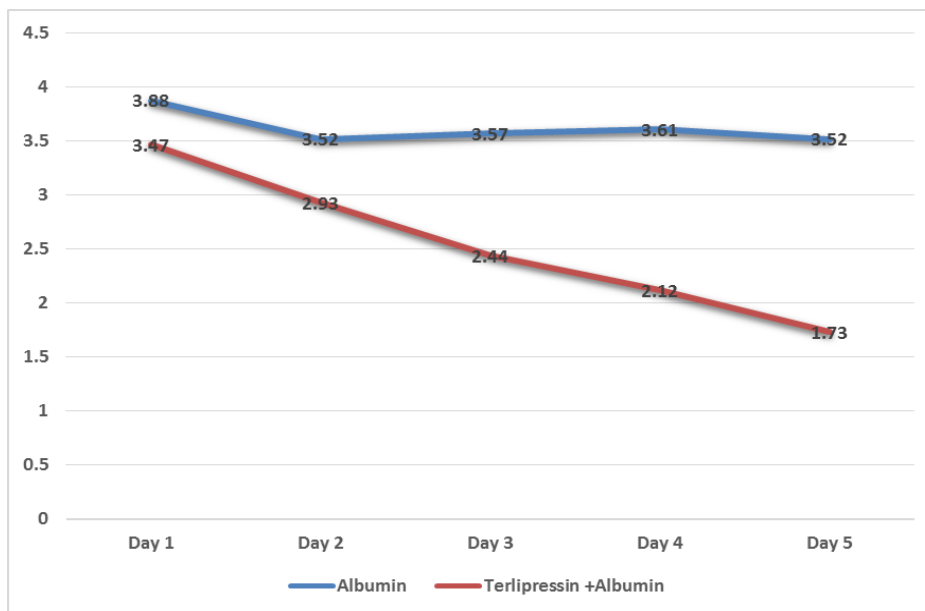
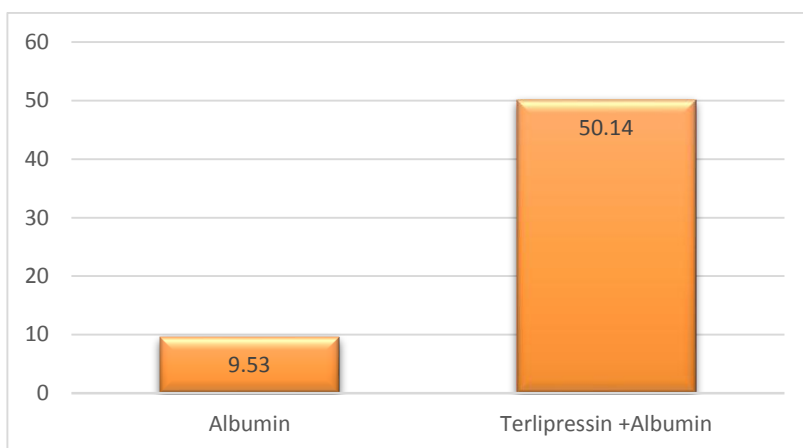


Figure 10 : Mean Percentage decrease of serum creatinine from day of admission and on 5th day



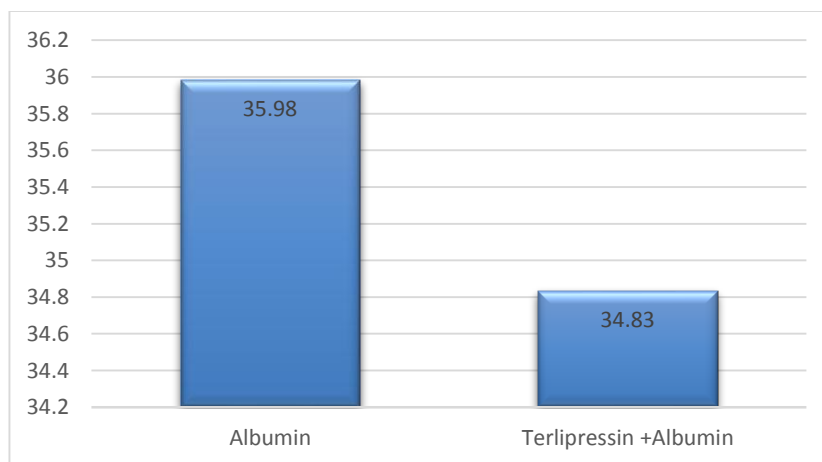
Study of Comparing MELD score in both the groups

In the present study on comparing the MELD score (Model for end stage liver disease). No significant difference was obtained in terms of MELD in both the treatment groups as revealed by the insignificant p value of 0.435. (Table 6, Figure 11)

Table 6 : Study of Comparing MELD score in both the groups

MELD	Treatment		Total	P value
	Albumin	Terlipressin +Albumin		
Mean	35.98	34.83	35.48	0.435
SD	2.85	3.98	3.42	

Figure 11: Comparing MELD



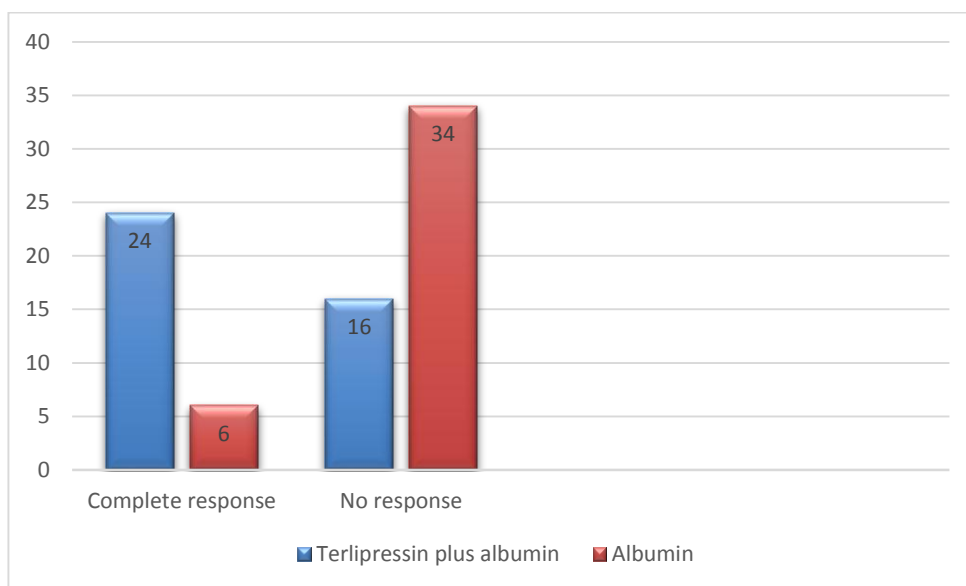
Study of Comparing treatment response in both groups

In the present study majority of the patients receiving Terlipressin +Albumin combination achieved complete response (60%) whereas only 40% had no response. Those receiving albumin alone, majority had no response (85%) and only 15% had shown complete response to treatment. The comparison was found to be significant with p value of 0.000032. (Table 7 , Figure 12)

Table 7: Comparing treatment response

Treatment	Complete response (%)	No response (%)	total	'P' value
Terlipressin plus albumin	24(60)	16(40)	40	0.000032
Albumin	6(15)	34(85)	40	
	30(37.5)	50(62.5)	80	

Figure 12 : Comparing treatment response



Discussion

Hepatorenal syndrome (HRS) is one of the most challenging complications of advanced liver disease, acute kidney injury, including HRS-1, is a significant predictor of mortality risk in these patients.^{62, 63} The magnitude and duration of increase in Serum Creatinine is associated directly with poorer patient outcomes before and after liver transplantation.^{64, 65} Reversing HRS-1 pretransplant has the potential for improving short-term patient survival pretransplant and reducing the need for Renal Replacement Therapy post-transplant.⁶⁶

Terlipressin is a synthetic vasopressin analogue with vasoconstrictor activity in the splanchnic and systemic vasculature.⁶⁷ This activity results in decreased portal blood inflow and reduced portal hypertension, the main cause of the hemodynamic abnormalities associated with advanced cirrhosis. The consequent redistribution of circulatory volume from the splanchnic to the systemic circulation improves systemic hemodynamics and increases renal perfusion pressure.^{68, 69} The increased effective arterial volume also decreases compensatory renal and systemic vasoconstrictor activities, further improving renal hemodynamics in these patients. The efficacy and safety of terlipressin in patients with HRS-1 have been evaluated in previous randomized, multicenter, placebo-controlled trials of varying sizes.^{4, 52, 53}

The present study compared Outcome between Patients of Hepatorenal Syndrome receiving Terlipressin plus Albumin and Albumin alone. This was single centre hospital-based cross-sectional, observational, descriptive study conducted in patients admitted to the Intensive Care Unit (ICU) of our institute over a period of 18 months from October 2019 to March 2021.

In the present study 80 subjects were divided equally into two groups of 40 each. One group of patients have received Terlipressin and albumin, while the other group has received only Albumin. In the present study no significant difference was obtained between the mean age and age distribution between two groups as revealed by the insignificant p value of 0.71. This confirms that the effect obtained in present study was not influenced by the age of the patients. Similar findings were concluded in study which was conducted by Sanyal AJ.⁵²

In the present study we also noted distribution of sex between two groups. No significant difference was obtained between the sex distribution between the treatment as revealed by the insignificant p value of 0.44. This confirms that the effect of intervention obtained in present study was not influenced by the sex of the patients. Similar findings were concluded in studies which were conducted by Francesco Salerno et al⁸, Pere Ginès et al⁷⁰, Mads Egerod Israelsen et al⁷¹.

In the present study we observed etiology distribution between two groups. Most common etiology in present study was alcohol (n=71). However, no significant difference was obtained in terms of distribution of etiology between the two groups as revealed by the insignificant p value of 0.79. In the present study we compared LFT parameters in both the groups. All the parameters including total Bilirubin, SGPT, INR and Sr. Albumin were found to be similar in both the groups except SGOT (p=0.002) which was found to be significantly lower in Terlipressin +Albumin treatment group (61.89±47.83) compared to albumin treatment alone (96.80±109.30). The findings of this present study were found to be similar in comparison to other studies conducted by Sanyal AJ⁵², Lise Lotte Gluud et al⁷², Khurram Jamil et al⁶⁷, Francesco Salerno et al⁸, Pere Ginès et al⁷⁰, Mads Egerod Israelsen et al⁷¹.

In the present study those who were treated with Terlipressin plus Albumin showed significant decrease in serum creatinine. A significant decrease in serum creatinine was observed on Day 5 (1.73±1.49) from Day 1 (3.47±1.68) making a percentage decrease of 50.14%. Whereas in the group receiving albumin only a

decrease of 9.53% was obtained. Moreover, the decrease in serum creatinine in albumin group was insignificant with p value of 0.237. The findings of the present study were found to be similar to a study by Martín-Llahí M et al⁴ which stated that in patients who responded to treatment with terlipressin and albumin, serum creatinine decreased from 256 ± 71 to 115 ± 18 micromol/L ($P = .005$) and mean arterial pressure increased from 75 ± 13 to 84 ± 18 mm Hg ($P = .02$). No significant changes were observed in these parameters in patients who did not respond to treatment with terlipressin and albumin (362 ± 195 vs 433 ± 248 micromol/L and 68 ± 10 vs 69 ± 12 mm Hg, respectively; $P = \text{ns}$ for both). Similarly Neri S et al⁵¹ observed that patients treated with terlipressin plus albumin showed a significant improvement, of renal function valued by creatinine (from 248 ± 96 to 112 ± 32 $\mu\text{mol/l}$) compared with patients treated with albumin alone (from 256 ± 104 to 188 ± 43 $\mu\text{mol/l}$); changes of serum creatinine were significantly different ($p=0.001$) between the two groups with worse values in patients treated with albumin alone ($p=0.001$).

In the present study we compared MELD between both the groups. No significant difference was obtained in terms of MELD in both the treatment groups as revealed by the insignificant p value of 0.435. The findings of the present study were found to be similar to a study by Martín-Llahí M et al⁴ which stated that there were no significant differences between the 2 groups with respect to the number of patients who were alive at 3 months, 6 in the terlipressin and albumin group (27%) and 4 in the albumin group (19%) ($P=0.7$). Similarly, Wong F et al³⁸ observed that the percentage of patients who received a liver transplant within 90 days after the first dose was lower in the terlipressin group than in the placebo group (23% versus 29%) despite there being no difference in MELD score between the two groups during the treatment period.

In the present study majority of the patients receiving Terlipressin plus Albumin combination achieved complete response (60%) whereas only (40%) had no response. Those receiving albumin alone, majority had no response (85%) and only (15%) had shown complete response to treatment. The comparison was found to be significant with p value of 0.000032. The findings of the present study were found to be similar to a study by Martín-Llahí M et al⁴ which stated that renal function improved in 43.5% of patients treated with terlipressin and albumin compared with only 8.7% of control patients treated with albumin alone ($P = .017$). Similarly, Neri S et al⁵¹ showed that in group A 21 patients (80%) showed a complete response to the therapy by terlipressin plus albumin, four patients (15%) showed a partial response, and one showed no response. In group B, five patients (19%) showed a complete response to therapy with only albumin, 11 (16%) partial response and 10 (30%) showed no response. These findings were consistent with our study.

Conclusion

In the present study it was concluded that the most common etiology was alcohol which was comparable to other studies also. All the parameters including total Bilirubin, SGPT (serum glutamic pyruvate transaminase), INR (International normalized ratio) and Serum Albumin were found to be similar in both the groups except SGOT (serum glutamate oxaloacetate transaminase) which was found to be

significantly lower in Terlipressin plus Albumin treatment group might suggest better safety profile. Statistically significant difference in serum creatinine was noted on admission and on 5th day of treatment suggesting better clinical and biochemical outcome in Terlipressin plus Albumin group. Complete response to treatment was significantly higher in Terlipressin and Albumin group compared to Albumin alone. Present study highlighted that the Terlipressin plus Albumin can be a better combination for treatment of hepatorenal syndrome.

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