Clinical Profile of Hepatorenal Syndrome: A Prospective Study

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ABSTRACT

Background and Objectives : The clinical profile of hepatorenal syndrome (HRS) patients admitted in a tertiary care hospital of Punjab was studied.

Methods : In this prospective study all the patients of chronic liver disease with renal involvement fulfilling the International Ascites Club criteria of HRS were evaluated over a period of one and a half year.

Result : Forty-two patients were diagnosed to have HRS and were included in the study. The incidence of HRS was 0.275% of hospital medical admissions. Alcoholic cirrhosis was the etiology in 71.5% of patients. Most of the patients of HRS received a combination of dopamine, albumin and terlipressin. The mortality rate was found to be approximately 60%. Variables amongst survival versus non-survival groups were analyzed. Oliguria and hepatic encephalopathy were more predominant in non-survival group. Serum bilirubin, hypoalbuminemia, hyponatremia, coagulopathy and urine osmolality was higher in non-survival group. Patients with Child-Pugh Score less than 10 had a better survival.

Conclusion : The poor prognostic factors in non-survival group were presence of ascites, severe jaundice, hepatic encephalopathy, alcohol abuse, hypoalbuminemia, progressive renal failure and a Child-Pugh Score > 10. Thus, HRS is not uncommon and needs proper diagnosis and prompt treatment to ensure better outcome.

Keywords : Hepatorenal syndrome, outcome, survival

INTRODUCTION

A wide array of circulatory changes occur in patients with liver cirrhosis and portal hypertension. Hepatorenal syndrome (HRS) is the development of renal failure in patients with advanced liver cirrhosis, who have portal hypertension and ascites, in the absence of kidney disease. The distinctive hallmark feature of HRS is the intense renal vasoconstriction caused by interactions between systemic and portal hemodynamics. This results in activation of vasoconstrictors and suppression of vasodilators in the renal circulation.[1] Histologically, kidneys are normal and kidney function is reversible with treatment. Although HRS usually occurs in patients with advanced cirrhosis, it has also been described in patients without ascites in the setting of acute fulminant hepatic failure.[2]

During the late 19th century, Frerichi and Flint made the original description of renal function disturbances in liver disease. In 1950's the clinical description of hepatorenal syndrome by Sherlock, Popper and Vessin emphasized the functional nature of the syndrome, the coexistence of systemic circulatory abnormalities and its dismal prognosis.

In 1996, the International Ascites Club described two different forms of HRS, type 1 and type 2. Although their pathophysiology is similar, but their manifestations and outcomes are different.[3]

Type 1 HRS is characterized by rapid doubling of serum creatinine to a level greater than 2.5 mg/dl or a halving of the creatinine clearance to less than 20 ml/min within two weeks and is precipitated most commonly by spontaneous bacterial peritonitis (SBP). It occurs in approximately 25% of patients with SBP, despite rapid resolution of the infection with antibiotics. Without treatment, median survival of patients with type I

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hepatorenal syndrome is less than 2 weeks and virtually all patients die within 10 weeks after the onset of renal failure.[3]

Type 2 HRS is characterized by a moderate and stable reduction in the glomerular filteration rate (with serum creatinine increasing to > 1.5 mg/dL or a creatinine clearance less than 40 ml/min). It most commonly occurs in patients with relatively preserved hepatic functions and median survival is 3-6 months. Although this is markedly longer than type 1 HRS, it is still shorter as compared to patient with cirrhosis and ascites who do not have renal failure.[4]

Watt *et al* [5] found that the most common predisposing factor for HRS was bacterial infection (48%), GI bleed (33%) and aggressive paracentesis (27%). Drugs (7%) and surgery (7%) were the precipitating causes. Twenty four percent (24%) of the patients with the HRS developed renal failure without an obvious cause.

Moreau *et al*[6] observed in 355 patients with cirrhosis and acute renal failure that 58% patients had pre-renal failure, one third of the patients had type 1 HRS, acute tubular necrosis in 41.7% and 1% had post renal (obstructive) acute renal failure. Until the recent development of effective therapies, the median survival following the development of type 1 HRS was 1.7 weeks, with 10% of the patients surviving more than 10 weeks. Survival rates in type two HRS is 50% at five years and 20% at one year. The most important aspect in the management of HRS is to prevent its recurrence. The latter is achieved by avoidance, prophylaxis, early recognition and treatment of precipitating factor. The data on profile of HRS from North India is scanty so this prospective study was undertaken to find the clinical profile of HRS.

MATERIAL AND METHODS

Forty-two (42) patients fulfilling the international ascites club criteria[1] of HRS were included in the study. The diagnosis of cirrhosis was based on history, examination, liver function tests, ultrasound abdomen and endoscopy. Etiology of cirrhosis was also noted. In all patients a history of jaundice, fever, abdominal pain, abdominal distension, decreased urine output, gastrointestinal bleed and altered sensorium was taken. Ascitic tap and blood cultures were taken to exclude gram negative septicemia and spontaneous bacterial peritonitis. Various variables were studied amongst the survivors and non-survivors to detect possible predictors of survival in HRS. A combination therapy of dopamine (1-5 µg/min), albumin and terlipressin (2 mg I/V 6hrly) was used in patients of HRS. Patients were followed up until their discharge or death. Institute's ethical committee approved this study.

Table I

Etiology of Chronic Liver Disease in HRS Patients

ETIOLOGY		NO. OF PATIENTS (%)
1.	Alcohol	30 (71.5)
2.	Post viral hepatitis a. HCV Related b. HbsAg Related	 10 (23.8) 02 (4.8)

STATISTICAL METHODS

The statistical methods included were the mean, percentage, standard deviation and students "t" test of significance.

RESULTS

Forty-two patients with HRS were included in our study. The incidence of HRS was 0.275% of hospital admissions. In the study, we found 95% male preponderance. They were all above 30 years of age with mean age of 47.7±9.8 years. Alcoholic cirrhosis constituted the commonest etiology of liver disease (71.5%) (Table I). The viral serology was positive in 28.5% of the patients, anti-HCV Ab in 23.8% and HBsAg in 4.8%.

The commonest symptom was jaundice (92.8%) followed by decreased urinary output (85.7%) and abdominal distension (71.4%). Altered sensorium was present in 61.9%, fever in 40.9%, pain abdomen (33%) and gastrointestinal bleed was seen in 25% of the patients. All the patients on endoscopy showed varices and had ascites on clinical examination. Icterus and asterixis was present in 92.8% and 74.4% cases respectively.

The bilirubin levels were 1.7-56 mg/dl (mean 21.6±13.6mg/dl). SGOT and SGPT were raised in more than 90% of the patients (Table II). The mean values of peak blood urea and peak serum creatinine were 125±75.36mg/dl and 4.6±2.4mg/dl respectively. Approximately 66.6% cases showed hyponatraemia. All the patients had bland urine sediment with urinary spot sodium of <20meq/l. Urine osmolality was greater than serum osmolality in all the patients (Table III). The

Table II

Liver Function Tests

INVESTIGATIONS	NO. OF PATIENTS	MEAN ± S.D.	RANGE
Serum Bilirubin	**42**	**21.63 ± 13.63**	**17-56.0**
SGOT			
≤ 40	2 (4.8%)	3.00 ± 14.14	20-40
> 40	40 (95.2%)	172.43 ± 111.72	46-598
p-value	<0.01		
T**otal**	**42**	**165.64 ± 113.22**	**20-598**
SGPT			
≤ 40	4(9.1%)	31.00 ± 9.76	17-39
> 40	38(90.9%)	106.26 ± 53.73	43-223
p-value	<0.01		
Total	**42**	**99.10 ± 55.79**	**17-223**
Alkaline Phosphatase			
≤ 120	13(30.9%)	100.97 ± 17.41	64-120
> 120	29(69.0%)	199.32 ± 83.39	122-574
p-value	<0.01		
Total	**42**	**168.88 ± 84.04**	**64-574**
Albumin			
≤ 3.5	41(97.6%)	2.07 ± 0.05	0.9 -3.3
> 3.5	01(2.4%)	3.8	3.8
p-value	<0.001		
Total	**42**	**2.11 ± 0.56**	**0.9-3.8**

Table III

Renal Function Tests

INVESTIGATIONS	NO. OF PATIENTS	MEAN ± S.D.	RANGE
Peak Blood Urea	42	125.50 ± 75.36	16-332
Peak Serum Creatinine			
< 1.4	0	0	0
> 1.4	42(100)	4.6 ± 2.4	2.5-10
p-value	<0.001		
Indices of Renal Failure			
Urine Routine			
Bland Sediment	42	-	-
Active Sediment	0	-	-
Urine Spot Sodium			
< 20	42	12.7 ± 6.3	1-18
> 20	0	-	-
p-value			<0.01
Serum Osmolality	42	274.90 ± 73.55	235-404
Urine Osmolality	42	843.70 ± 140.47	688-1000

mortality rate was found to be approximately 60% (Table IV). The patients who left against medical advice were terminally sick and had very poor prognosis and were included among non-survivors. In our study, about 60% of patients were treated with combination of albumin infusion, dopamine infusion and terlipressin followed by albumin and dopamine in 33% patients and dopamine infusion alone in 7% patients.

Various variables between survival and non-survival groups were compared (Table V). Oliguria was predominant in the non-survival group (96%). Jaundice was present in all the patients of both the groups. Hepatic encephalopathy was present in 61.9% of patients, predominantly in the non-survival group. Hypoalbuminaemia and hyponatraemia was more pronounced in non-survival group. Serum bilirubin levels were found to be significantly higher in the non-survival group as compared to survival group. Serum creatinine was found to be insignificantly higher in non-survival group. Ratio of urine osmolality and serum osmolality was higher in non-survival group .Significant number of patients had history of alcohol abuse among the non-survivals. Therapy with albumin, dopamine and terlipressin was found to effective in those with Child-Pugh Score<10. Jaundice, renal failure, hepatic encephalopathy and ascites were found to be poor prognostic factors with significant p value. Patients with Child-Pugh Score<10 had a better survival advantage.

DISCUSSION

This prospective study included forty-two patients of HRS. These patients constituted about 0.275% of medical admission. There was male (95%) preponderance in our study with mean age of patients of HRS being 47.69 ± 9.75 years. This was similar to studies conducted by Butt *et al* where mean age of patients was 51.7+11.3 years and 65% of patients enrolled were male.[7] Salerno *et al* also studied 134 cirrhotics in which the mean age was 61.3+9.6 years and 73% of patients were male.[8]

The clinical symptomatology in our patients showed that most of them presented with jaundice (92.9%), decreased urine output (85.7%) and hepatic encephalopathy (71.4%). Fever was present in 40% of patients and gastrointestinal bleed in 32%. These presentations were similar to cases observed by Epstein *et al*[9] where most of the patients had clinical ascites and renal failure at presentation. In our study, we found that all our patients of HRS had ascites, 92.9% of the patients had icterus, significant percentage had asterixis and history of alcohol abuse. Similar results were seen in studies conducted by Watt *et al*.[5]

We found raised bilirubin levels (mean value 21.63 ± 13.63 mg/dL and raised SGOT and SGPT in more than 90% of the patients. Serum alkaline phosphatase was raised in 69% of the patients included in the study. Almost all of our patients (97.6%) had hypoalbuminaemia. Coagulopathy was present in more than 90% of the patients. Urine osmolality and serum osmolality ratio was found to be more than one. These findings corroborated with clinical studies conducted by Procel A *et al.*[10] Approximately 40% of HRS cases were discharged from the hospital in satisfactory condition. Remaining either died in the hospital or left against medical advice due to poor prognosis. On comparison of the variables, amongst survivors versus non-survivors, we found that administration of albumin, dopamine and terlipressin to patients who had Child-Pugh Score < 10 at presentation showed reversal of HRS. Twelve (64.7%) patients amongst survivors benefited from the therapy while 52% of the patients amongst nonsurvivors received this therapy but did not improve and the Child-Pugh score in this group was found to be greater than 10. The beneficial effect of terlipressin was similar to study conducted by Uriz *et al*[11] and Hadengue *et al.*[12]

We compared the various variables in HRS to find the predictive factors and outcome in survival and non-survival groups. Oliguria was found in 96% of the patients of non-survival group, jaundice was present in 100% of these patients. Higher levels of serum bilirubin (25.09 ± 13.7 mg/dL) were found in non-survivors compared to a mean value of 16.54 ± 12.19 mg/dL in survivors. Sixty eight percent of patients who did not survive had hepatic encephalopathy. Decreased levels of albumin were present in non-survivors as compared to survivors. Hyponatraemia was more pronounced amongst the non-survival group. Patients in the non-survival group had significant coagulopathy as compared to survivors. The mean urine spot sodium for non-survivors was found to be less as compared to survivors. Urine osmolality and plasma osmolality ratio was found to be greater in the non-survivor group (3.24 ± 2.16). Significant alcohol abuse was a predominant factor in non-survivors (84%).

On statistical analysis, the severity of jaundice, presence of oliguria, hepatic encephalopathy and refractory ascites were poor prognostic factors in patients of HRS. Also Child-Pugh Score >10 had poor prognostic

value among the non-survivors. The prognostic value of Child-Pugh Score in HRS was similar to studies conducted by Colle *et al*[13] and Moreau *et al.*[6] Once considered fatal with mortality of greater than 90%, in hepatorenal syndrome there is improved prognosis with therapies including terlipressin, dopamine and albumin infusion.

CONCLUSION

Decompensated alcoholic cirrhosis is the commonest cause of HRS. HRS is not uncommon and with judicious treatment, especially using terlipressin with albumin a significant number of patients can be cured. The poor prognostic factors in HRS are presence of ascites, severe jaundice, hepatic encephalopathy, alcohol abuse, hypoalbuminaemia, progressive renal failure and a Child-Pugh Score >10.

REFERENCES

1. Turban S, Thuluvath PJ, Atta MG. Hepatorenal syndrome. World J Gastroenterol 2007;13(30):4046-55.
2. Wilkinson SP, Blendis LM, Williams R. Frequency and type of renal and electrolyte disorders in fulminant hepatic failure. Br Med J 1974;1:186-9.
3. Santiago JM. The hepatorenal syndrome. Med Clin North Am 2008;92(4):813-37.
4. Arroyo V, Fernandez J, Gines P. Pathogenesis and treatment of hepatorenal syndrome. Semin liver dis 2008;28(1):81-95.
5. Watt K, Uhanova J, Minuk GY. Hepatorenal syndrome:diagnostic accuracy, clinical features, and outcome in a tertiary care centre. Am J Gastroenterol 2002;97(8):2046-50.
6. Moreau R, Durand F, Poynard T, Duhamel C, Cervoni JP, Ichaï P, *et al*. Terlipressin in patients with cirrhosis and type 1 HRS: A retrospective multicenter study. Gastroenterol 2002;122(4):923-30.
7. Butt AK, Khan AA, Alam A, Shah SW, Shafqat F, Naqvi AB. Predicting hospital mortality in cirrhotic patients: comparison of Child-Pugh and Acute Physiology, Age and Chronic Health Evaluation (APACHE III). Am J Gastroenterol 1998;93(12):2469-75.
8. Solerno F, Barroni G, Moser P, Badalamenti S, Cassarà L, Maggi A, *et al*. Survival and prognostic factors of cirrhotic patients with ascites; a study of 134 patients. Am J Gastroenterol 1993;88(4):514-9.
9. Epstein M, Berk DP, Hallenberg NK, Adams DF, Chalmers TC, Abrams HL, *et al*. Renal failure in the patients with cirrhosis; the role of active vasoconstriction. Am J Med 1970;49(2):175-85.
10. Porcel A, Diaz F, Rendon P, Macias M, Martin-Herrera L, Giron-Gonzalez JA. Dilutional hyponatremia in patients with cirrhosis and ascites. Arch Intern Med 2002;162(3):323-8.
11. Uriz J, Gines P, Cardenas A, Sort P, Jimenez W, Salmeron JM, *et al*. Terlipressin plus albumin infusion: an effective and safe therapy of hepatorenal syndrome. J Hepatol 2000;33(1):43-8.
12. Hadengue A, Gadano A, Moreau R, Giostra E, Durand F, Valla D, *et al*. Beneficial effects of the 2-day administration of terlipressin in patients with cirrhosis and hepatorenal syndrome. J Hepatol 1998;29(4):565-70.
13. Colle I, Durand F, Pessione F, Rassiat E, Bernuau J, Barriere E, *et al*. Clinical course, predictive factors and prognosis in patients with cirrhosis and type 1 hepatorenal syndrome treated with terlipressin: a retrospective analysis. J Gastroenterol Hepatol 2002;17(8):882-8.