Gastroenterology & Hepatology Journal (GHJ)

Research Article

Terlipressin Vs Human Albumin Infusion in Treating Type 2 Hepatorenal Syndrome

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Abstract

Background: Hepatorenal syndrome (HRS) is the development of progressive renal failure in patients with advanced chronic liver disease, occasionally fulminant hepatitis, who have marked circulatory dysfunction, the definitive treatment for hepatorenal syndrome is Liver transplantation, and all other therapies can best be described as bridges to transplantation. Systemic vasoconstrictors are the most promising pharmacologic agents in the management of HRS.

Objectives: The aim of the work was to evaluate the precipitative factors in cirrhotic patients who developed hepatorenal syndrome and to evaluate the role of terlipressin in the treatment of hepatorenal syndrome (type 2)

Patients and Methods: the study was conducted on 40 cirrhotic patients with hepatorenal syndrome (type II), randomized into two groups: Group I consisted of 20 patients who were given terlipressin, 1mg/8h, intravenous infusion (3mg/day) for 7days, in additional to conventional treatment of hepatorenal syndrome (intra venous albumin 1g/kg/day up to 100gm/day).Group II consisted of 20 patients who were given only conventional treatment of hepatorenal syndrome (intra venous albumin) and was considered as a control group. All patients were subjected to the following: Detailed history taking and proper clinical examination.

- Arterial blood pressure and urine output.

- Laboratory investigations (complete urine analysis, complete blood count, liver function tests (ALT, AST, serum albumin, prothrombin time and activity, serum bilirubin (total and direct), renal function tests (blood urea and serum creatinine), seum Na, K, Urinary Na and ascitic fluid analysis.

- Ultasound examination of abdomen.

Blood urea and serum creatinine, serum Na, K, Urinary Na were re-evaluated after 7 days of treatment.

Results: The result of the present study showed that few patients had evident precipitating factors for HRS including hematemesis in three patients and spontaneous bacterial peritonitis in one patient. After follow up for 7days renal function improved in patients with terlipressin treatment (fall in serum creatinine below 1,5 mg\dl), there was no change in renal functions in control group. There were no ischemic side effects in patients with terlipressin treatment.

Conclusions: Terlipressin improves renal functions in patients with hepatorenal syndrome (type 2). The use of Terlipressin as a therapeutic option in patients with hepatorenal syndrome was not associated with significant short term adverse effects. Most of patients with type 2 hepatorenal syndrome have no identifiable precipitative factors.

Key words: *Hepatorenal Syndrome, Terlipressin.*

Introduction

Hepatorenal syndrome is a life-threatening medical condition that consists of rapid deterioration in renal function in individuals with cirrhosis, fulminant liver failure, severe alcoholic hepatitis, or (less often) metastatic tumors [1].

Based upon the rapidity of the decline in renal function, two forms of hepatorenal syndrome have been described.

Type 1 hepatorenal syndrome – is more serious; it is defined as doubling of the initial serum creatinine concentrations to a level greater than 226 µmol/L (2.5 mg/dL) in less than 2 weeks.

Type 2 hepatorenal syndrome – is characterized by moderate renal failure (serum creatinine 133-226 µmol/L or 1.5- 2.5 mg/dL), with a steady or slowly progressive course [2].

Hepatorenal syndrome is common, with a reported incidence of 10% among hospitalized patients with cirrhosis. In decompensated cirrhosis, the probability of developing HRS with ascites ranges between 8-20% per year and increases to 40% at 5 years. An estimated 35-40% of patient with end-stage liver disease and ascites will develop HRS. People of all races who have chronic liver disease are at risk for HRS. Frequency is equal in both sexes; most patients with chronic liver disease are in their fourth to eighth decades of life. Type 1 hepatorenal syndrome (HRS) has a median survival of 2 weeks, with few patients surviving more than 10 weeks. Type 2 HRS has a median survival of 3-6 months. The onset of renal failure is typically insidious but can be precipitated by an acute insult, such as bacterial infection or gastrointestinal bleeding. Spontaneous bacterial peritonitis can trigger progressive hepatorenal syndrome [3,4].

The renal failure in hepatorenal syndrome is believed to arise from abnormalities in blood vessel tone in the kidneys. The predominant theory is that blood vessels in renal circulation are constricted secondary to splanchnic vasodilataion, which is mediated by factors released by liver disease. Nitric oxide, prostaglandins, and other vasoactive substances have been hypothesized as powerful mediators of splanchnic vasodilation in cirrhosis. The consequence of this phenomenon is a decrease in the "effective" volume of blood sensed

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Received: January 27, 2018; **Accepted:** February 17, 2018; **Published:** February 20, 2018.

by the juxtaglomerular apparatus, leading to the secretion of renin and the activation of the renin-angiotensin system, which results in the vasoconstriction of vessels in the systemic circulation and in the kidney specifically. However, the effect of this is insufficient to counteract the mediators of vasodilation in the splanchnic circulation, leading to persistent "underfilling" of the kidney circulation and worsening kidney vasoconstriction, leading to renal failure [5].

Many other diseases of the kidney are associated with liver disease and must be excluded before making a diagnosis of hepatorenal syndrome, these include; individuals with pre-renal failure, acute tubular necrosis (ATN), drug toxicity (e.g. aminoglycoside antibiotics, non-steroidal anti-inflammatory drugs, and antiviral therapy), renal failure due to radiocontrast agents, obstructive uropathy and glomerulonephritis in patients with hepatitis B or C [6].

The definitive treatment for hepatorenal syndrome is liver transplantation, and all other therapies can best be described as bridges to transplantation. Systemic vasoconstrictors are the most promising pharmacologic agents in the management of HRS. They rely on the assumption that interrupting the splanchnic vasodilation will subsequently relieve the intense renal vasoconstriction. Studied vasoconstrictors include vasopressin analogues (ornipressin and terlipressin), somatostatin analogue (octreotide), and the α-adrenergic agonists (midodrine and norepinephrine) [7].

Patients and Methods

The study was conducted on 40 cirrhotic patients with hepatorenal syndrome (type II), randomized into two groups: **Group I** consisted of 20 patients who were given terlipressin, 1mg/8h, intravenous infusion (3mg/day, terlipressin vial 1mg→5ml) for 7days, in additional to conventional treatment of hepatorenal syndrome (intra venous albumin 1g/kg/day up to 100gm/day, a bottle of 50ml contains 10gm of albumin). **Group II** consisted of 20 patients who were given only conventional treatment of hepatorenal syndrome (intra venous albumin) and was considered as a control group.

All patients were subjected to the following:

1. Detailed history taking, and proper clinical examination.

-History of (viral hepatitis (B, C), schistosomiasis, nonalcoholic fatty liver, alcoholic hepatitis, hereditary liver disease (hereditary hemochromatosis, Wilson's disease), autoimmune hepatitis or hepatotoxic drugs),

- Presence of complications (jaundice, ascites, hepatic encephalopathy or gastrointestinal bleeding (melena, hematemesis).

-Arterial blood pressure.

-Assessment of urine output.

-Presence of precipitating factors: (gastrointestinal bleeding, large volume paracentesis, spontaneous bacterial peritonitis and other infections).

2. Laboratory investigations which include:

A. Complete Urine analysis (Osmolality, RBC's, Protein and Casts).

B. Complete blood count.

C. Liver function tests (ALT, AST, serum albumin, prothrombin time and activity, and serum bilirubin (total and direct).

D. Renal function tests (blood urea and serum creatinine).

E. Serum Na, K.

F. Urinary Na.

G. Ascitic fluid analysis:

-Gross appearance.

-Biochemistry (total protein, albumin, glucose, tumor markers "alfaprotein" (AFP)).

-Microscopic examination (red blood cell count, white blood cell count, and white blood cell differential count).

3. Ultrasound examination of the abdomen paying particular stress to renal parenchymal disease and urinary tract obstruction and to the liver (cirrhosis, ascites and portal hypertension).

Follow up of the patients: after 7 days

1. Complete urine analysis.

2. Complete blood count.

3. Renal function tests (blood urea and serum creatinine).

4. Serum Na, K.

5. Urinary Na.

Statistical Analysis

Was done using IBM SPSS software package version 20.0. Qualitative data were described using number and percent. Quantitative data were described using range (minimum and maximum), mean, standard deviation and median. Significance of the obtained results was judged at the 5% level.

Results

Demographic data: (Table 1)

Patients with HRS included in the study showed no sex predilection and all patients included in the study were in their 5th to 8th decades of life (age ranges from 50 to 71 years). No significant differences as regard age or sex were detected between cases and control.

History and Clinical examination (Table 2)

All patients included in the study were suffering of HCV infection

Table 1: Comparison between the studied groups according to demographic data.

	Cases (n = 20)		Control (n = 10)		Test of Sig.	P
	No.	%	No.	%		
Sex						
Male	8	40.0	6	60.0	χ^2= 1.071	^{FE}p= 0.442
Female	12	60.0	4	40.0		
Age						
Min. – Max.	50.0 – 71.0		55.0 – 68.0		t= 0.685	0.499
Mean ± SD.	61.65 ± 5.94		63.10 ± 4.31			
Median	63.0		64.50			

χ^2, p:χ^2 and p values for Chi square test for comparing between the two groups
FE: Fisher Exact for Chi square test
t: Student t-test

Table 2: Comparison between the studied groups according to sign and symptoms.

Signs and symptoms	Cases (n = 20)		Control (n = 10)		χ^2	P
	No.	%	No.	%		
Ascites						
Moderate	12	60.0	6	60.0	0.0	^{FE}p=1.000
Tense	8	40.0	4	40.0		
Jaundice	20	100.0	10	100.0	-	-
Hepatic encephalopathy	20	100.0	10	100.0	-	-
Hematemsis	2	10.0	1	10.0	0.0	^{FE}p=1.000

χ^2, p:χ^2 and p values for Chi square test for comparing between the two groups
FE: Fisher Exact for Chi square test

and all have ascites, jaundice and history of hepatic encephalopathy. No significant difference between both groups as regard clinical manifestations.

Precipitating Factors (Table 3)

Three patients in both groups (10%) had gastrointestinal hemorrhage (hematemesis), while only one patient had spontaneous bacterial peritonitis as a precipitating factor.

Blood pressure (Table 4)

Blood pressure of patients included in the study ranged between 80-110 for systolic pressure and 50-70 for diastolic pressure. There was no significant difference between both groups as regard blood pressure.

Table 3: Comparison between the studied groups according to the presence of precipitating factors.

	Cases (n = 20)		Control (n = 10)		χ^2	^{FE}p
	No.	%	No.	%		
Gastrointestinal hemorrhage						
Hematemsis	2	10.0	1	10.0	-	-
Melena	0	0.0	0	0.0		
Spontaneous bacterial peritonitis	1	5.0	0	0.0	0.517	1.000
Large volume paracentesis without albumin infusion	0	0.0	0	0.0	-	-

χ^2, p: χ^2 and p values for Chi square test for comparing between the two groups
FE: Fisher Exact for Chi square test

Table 4: Comparison between the studied groups according to blood pressure.

Blood pressure	Cases (n = 20)	Control (n = 10)	T	P
Systolic				
Min. – Max.	80.0 – 110.0	80.0 – 100.0	0.569	0.574
Mean ± SD.	93.0 ± 9.23	91.0 ± 8.76		
Median	95.0	90.0		
Diastolic				
Min. – Max.	50.0 – 70.0	50.0 – 70.0	0.202	0.841
Mean ± SD.	61.50 ± 5.87	61.0 ± 7.38		
Median	60.0	60.0		

t: Student t-test

Liver function tests (Table 5)

All patients included in the study showed impairment in liver functions, total serum bilirubin ranged from 2.5-6.0mg/dl while direct serum bilirubin ranged from 1.80-5.0 mg/dl. SGPT ranged from 48– 185 u/l and SGOT ranged from 35– 309 u/l. Serum albumin ranged from 1.80 – 2.80g/dl, Prothrombin time ranged from16.80 – 48.90Sec. and Prothrombin Activity ranged from 14.90– 56.0%. No significant differences were detected between both groups as regard liver functions.

Renal functions (Table 6 and 7)

1- Urine output

All patients included in the study showed normal urine output ranging from 1000-2000 ml/day. Oliguria was not detected in any patient. No significant difference was detected between both groups as regard urine output.

2- Blood urea and serum creatinine:

Table 7 shows measurement of blood urea and serum creatinine in the studied groups on the 1st day of admission and after 7 days. On the 1st day, mean blood urea in group I was 128.10 ± 30.97 mg/dl, while in group II it was 133.50 ± 15.28 mg/dl and mean serum creatinine was 2.58 ± 0.76 in group I and 2.49 ± 0.54 in group II.

Table 5: Comparison between the studied groups according to liver function tests.

	Cases (n = 20)	Control (n = 10)	Test of Sig.	P
Serum bilirubin (mg/dl)				
Total				
Min. – Max.	2.50 – 6.0	3.0 – 5.0	Z = 0.620	0.535
Mean ± SD.	4.54 ± 1.35	4.50 ± 0.71		
Median	4.95	4.75		
Direct				
Min. – Max.	1.80 – 3.50	2.0 – 3.20	Z = 0.491	0.623
Mean ± SD.	2.74 ± 0.64	2.88 ± 0.39		
Median	2.90	3.0		
SGPT (u/l)				
Min. – Max.	48.0 – 185.0	55.0 – 85.0	Z = 0.198	0.843
Mean ± SD.	78.50 ± 38.12	70.60 ± 10.13		
Median	70.50	71.0		
SGOT (u/l)				
Min. – Max.	35.0 – 309.0	60.0 – 125.0	Z = 0.198	0.843
Mean ± SD.	98.95 ± 64.18	86.70 ± 23.75		
Median	83.50	80.0		
Serum albumin(g/dl)				
Min. – Max.	1.80 – 2.80	1.80 – 2.50	t = 0.457	0.651
Mean ± SD.	2.19 ± 0.35	2.13 ± 0.31		
Median	2.0	2.0		
Prothrombin time (Sec.)				
Min. – Max.	16.80 – 48.90	17.50 – 46.0	Z = 0.286	0.775
Mean ± SD.	30.85 ± 12.71	28.76 ± 9.54		
Median	28.50	27.25		
Prothrombin Activity%				
Min. – Max.	14.90 – 56.0	18.50 – 54.0	Z = 0.684	0.494
Mean ± SD.	39.91 ± 14.10	38.15 ± 12.28		
Median	46.0	40.25		

t: Student t-test Z: Z value for Mann Whitney test
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Table 6: Comparison between the studied groups according to urine output /day.

Urine output /day(ml/day)	Cases (n = 20)	Control (n = 10)	t	P
Min. – Max.	1000.0 – 2000.0	1400.0 – 1800.0	0.661	0.514
Mean ± SD.	1575.0 ± 242.52	1520.0 ± 139.84		
Median	1600.0	1500.0		

t: Student t-test

Table 7: Comparison between the studied groups according to renal function.

		Cases (n = 20)	Control (n = 10)	t	P
Blood urea (mg/dl)	**1st day**				
	Min. – Max.	80.0 – 197.0	110.0 – 165.0	0.517	0.609
	Mean ± SD.	128.10 ± 30.97	133.50 ± 15.28		
	Median	126.50	130.0		
	7th days				
	Min. – Max.	45.0 – 80.0	110.0 – 155.0	16.041*	<0.001*
	Mean ± SD.	56.15 ± 11.77	129.50 ± 11.89		
	Median	54.50	130.0		
	^{t}p	<0.001*	0.113		
Serum creatinine (mg/dl)	**1st day**				
	Min. – Max.	1.80 – 4.20	1.80 – 3.40	0.315	0.755
	Mean ± SD.	2.58 ± 0.76	2.49 ± 0.54		
	Median	2.40	2.40		
	7th days				
	Min. – Max.	1.0 – 1.40	2.0 – 3.50	6.957*	<0.001*
	Mean ± SD.	1.21 ± 0.16	2.49 ± 0.57		
	Median	1.20	2.35		
	^{t}p	<0.001*	1.000		

t: Student t–test for comparing between the two studied groups
^{t}p: p value for Paired t–test for comparing between 1st day and 7th days in each group
*: Statistically significant at $p \leq 0.05$

No significant difference between both groups as regard blood urea and serum creatinine on 1st day of admission.

After 7 days, there was no significant difference in blood urea and serum creatinine in group II (control), compared to day 1. Blood urea ranged from 110.0 – 155.0 mg/dl and serum creatinine ranged from 2.0 – 3.50mg/dl.

Whereas in group I there was a significant improvement in blood urea and serum creatinine, compared to both day 1 values of the same group and day 7 results of control group. Blood urea declined to reach a mean of 56.15 ± 11.77 mg /dl and serum creatinine declined mean value reached 1.21 ± 0.16 mg/dl.

Serum electrolytes (Table 8)

Serum Na, Serum K and Urinary Na were measured in the studied groups on the 1st day of admission and after 7 days. On the 1st day, there was a decrease in Serum Na in both groups. Serum Na ranged from 125.0 to 129.0mmol/l, whereas Serum K was normal in both groups ranging from 3.50 to 5.10mmol/l, urinary Na was decreased in both groups. Urinary Na ranged from 5.0 to 8.0 meq/l/ 24h. No significant difference between both groups as regard Serum Na, Serum K and Urinary Na on the 1st day of admission.

On the 7th day, there were no significant differences in Serum Na, serum K and Urinary Na in control group compared to day 1, Serum Na ranged from 125.0 to 128.0 mmol/l, while Serum K ranged from 3.50 to 5.0 mmol/l and Urinary Na ranged from 5.0 to 8.0meq/l/24h.

Whereas in cases, there was a significant increase in serum Na compared to day 1 results of same group as well as day 7 results of control group. It ranged from 130.0 to 132.0mmol/l, and serum K ranged from 3.50 to 5.10mmol/l. Significant increase in Urinary Na was also noted as it ranged from 9.0 to 14.0meq/l/24h, compared to day 1 result of the same group as well as day 7 results of the control group.

Table 8: Comparison between the studied groups according to serum Na, serum K and urinary Na, ischemic side effects in patients with terlipressin treatment.

		Cases (n = 20)	Control (n = 10)	t	P
Serum Na (mmol/l)	**1st day**				
	Min. – Max.	125.0 – 129.0	125.0 – 129.0	0.372	0.713
	Mean ± SD.	126.90 ± 1.37	126.70 ± 1.42		
	Median	126.0	126.0		
	7th days				
	Min. – Max.	130.0 – 132.0	125.0 – 128.0	8.384*	<0.001*
	Mean ± SD.	130.40 ± 0.68	126.40 ± 1.43		
	Median	130.0	126.0		
	tp	<0.001*	0.081		
Serum K (mmol/l)	**1st day**				
	Min. – Max.	3.50 – 5.10	3.50 – 5.0	0.364	0.719
	Mean ± SD.	4.23 ± 0.61	4.31 ± 0.59		
	Median	4.10	4.30		
	7th days				
	Min. – Max.	3.50 – 5.10	3.50 – 5.0	0.021	0.983
	Mean ± SD.	4.23 ± 0.61	4.22 ± 0.60		
	Median	4.10	4.20		
	tp	-	0.041*		
Urinary Na (meq/l/24h)	**1st day**				
	Min. – Max.	5.0 – 8.0	5.0 – 8.0	0.308	0.760
	Mean ± SD.	6.35 ± 1.27	6.20 ± 1.23		
	Median	6.0	6.0		
	7th days				
	Min. – Max.	9.0 – 14.0	5.0 – 8.0	7.900*	<0.001*
	Mean ± SD.	11.10 ± 1.83	6.0 ± 1.25		
	Median	11.0	5.50		
	tp	<0.001*	0.168		

t: Student t–test for comparing between the two studied groups
tp: p value for Paired t–test for comparing between 1st day and 7th days in each group
*: Statistically significant at $p \leq 0.05$

Discussion

Hepatorenal syndrome (HRS) is the development of progressive renal failure in patients with advanced chronic liver disease, occasionally fulminant hepatitis, who have marked circulatory dysfunction [1, 8-10]. The onset of renal failure is typically insidious but can be precipitated by an acute insult, such as bacterial infection, gastrointestinal bleeding and large-volume paracentesis without albumin infusion [11,12]. The definitive treatment for hepatorenal syndrome is Liver transplantation, and all other therapies can best be described as bridges to transplantation. Systemic vasoconstrictors are the most promising pharmacologic agents in the management of HRS [13, 14].

The aim of the present work was to evaluate the precipitating factors in cirrhotic patients who developed hepatorenal syndrome and to evaluate the role of terlipressin in the treatment of type II hepatorenal syndrome.

Diagnosis of cases of HRS was done depending on both major and minor criteria:

Major Criteria

1. Low glomerular filtration rate, as indicated by serum creatinine greater than 1.5 mg/dl or 24-hour creatinine clearance lower than 40 ml/minute.
2. Absence of shock, ongoing bacterial infection, fluid losses and current treatment with nephrotoxic drugs.
3. No sustained improvement in renal function (decrease in serum creatinine to 1.5 mg/dl or less or increase in creatinine clearance to 40 ml/minute or more) following diuretic withdrawal and expansion of plasma volume with 1.5 l of a plasma expander.
4. Proteinuria lower than 500 mg/day and no ultrasonographic evidence of obstructive uropathy or parenchymal renal disease.

Additional Criteria

1. Urine volume lower than 500 ml/day
2. Urine sodium lower than 10 mEq/l
3. Urine osmolality greater than plasma osmolality
4. Urine red blood cells less than 50 per high-power field
5. Serum sodium concentration lower than 130 mEq/l

All major criteria must be present for the diagnosis of hepatorenal syndrome. Additional criteria are not necessary for the diagnosis, but provide supportive evidence. The result of the present study showed that only 3 patients had hematemesis, 1 patient had spontaneous bacterial peritonitis. No precipitating factors were identified in the rest of the patients.

Kim et al., [15] determined that spontaneous bacterial peritonitis was observed concomitantly in 29 (36%) out of 80 patients with hepatorenal syndrome. Among our patients, spontaneous bacterial peritonitis was observed with hepatorenal syndrome in only one patient and this is due to limited number of patients in our study. While Fernandez J et al, study showed that spontaneous bacterial peritonitis was present in 10 patients with HRS out of 30 and only in 2 patients out of 30 who used a norefloxacin prophylaxis. In the study conducted by Fasolato et al., [16] spontaneous bacterial peritonitis was observed concomitantly with hepatorenal syndrome in 35

patients (33.6%).

Cárdenas et al., [17] found that renal impairment occurred in 11% of 175 of HRS patients that experienced gastrointestinal bleeding. In our study, gastrointestinal bleeding (hematemesis) was determined in 3 patients. Ginès et al., [18] found that large volume paracentesis without albumin infusion precipitated HRS in 21% of 53 cases. In contrast, there were no cases of HRS when large volume paracentesis was performed with intravenous albumin replacement. In our study large volume paracentesis without intravenous albumin replacement, was not determined in any patients.

After follow up for 7days, renal functions improved in patients with Terlipressin treatment (group1) (fall in serum creatinine below 1.5 mg\dl) there were no changes in renal functions in control group. There were no ischemic side effects in patients with terlipressin treatment.

In agreement with the present study, Sanyal et al. [19] carried out six randomized clinical trials involving patients with hepatorenal syndrome to assess the beneficial effects of terlipressin alone or with albumin versus placebo, no intervention or albumin for hepatorenal syndrome. Five trials assessed terlipressin (with albumin in three trials) versus no intervention (with albumin in three trials) and one trial assessed terlipressin versus albumin. In total, 74 of 155 (47.7%) patients randomized to terlipressin alone or terlipressin with albumin versus 98 of 154 (63.6%) patients randomized to no intervention, placebo or albumin. Random-effects model meta-analysis found that Terlipressin improves renal functions (reduced serum creatinin <1.5 mg /dl).

A meta-analysis of controlled clinical trials by Fabrizi et al., [20] to evaluate the efficacy and safety of terlipressin in patients with HRS included five studies involving 243 unique patients with HRS. Pooling of study results showed a significant increase in HRS reversal among study (terlipressin) versus control (placebo) patients. The meta-analysis showed that terlipressin has higher efficacy than placebo in reversing renal function in the HRS population. There was no apparent impact of terlipressin therapy on survival in HRS patients but further large-size trials are needed. Terlipressin use in the HRS population requires careful selection of patients and close clinical surveillance. These results support the use of terlipressin for reversal of renal function in the HRS population. Thus, the use of Terlipressin has been shown to be safe, with minimal side effects that usually disappear after dose reduction, and results in an improved outcome in patients with HRS.

This is was postulated also by Ortega R et al, who concluded that, the administration of the vasopressin analogue Terlipressin improves renal function in patients with cirrhosis and HRS and is able to reverse HRS in approximately 60% of patients. The reversal of HRS is associated with an improved survival. The same author reported in another study [21] that long-term therapy with terlipressin and albumin is beneficial as a bridge to liver transplant. Nevertheless, recovery of renal function can be achieved in less than 50% of patients with HRS after terlipressin use and the recovery of renal function may also be partial in patients who are defined full responders. The authors also concluded that renal replacement therapy should not be considered a first-line therapy for HRS.

In agreement with the present study Hadengue et al., [22] carried out a double-blind, crossover, randomized study on 9 patients with HRS. Patients received terlipressin and a placebo for 2 days in a randomized order. Terlipressin administration significantly decreased serum creatinine, Terlipressin administration significantly decreased plasma concentrations of renin and aldosterone but not atrial natriuretic peptide levels, and these biochemical changes were not seen in the placebo group.

Solanki et al., [23] conducted a randomized, controlled, single-blind trial. They assigned 24 consecutive patients with HRS to treatment with terlipressin 1 mg IV at 12 h intervals (12 patients in group A) or placebo (12 patients (group B). The end-point of the study was improvement in renal function defined as reversal of HRS and survival at 15 days. Terlipressin administration was associated with transient self-limiting side-effects including crampy abdominal pain in two patients and cardiac arrhythmias in three patients. Five of the 12 patients survived in group A compared with none in group B at day 15 ($P < 0.05$) and all survivors had reversal of HRS. They concluded that terlipressin significantly improves renal functions and systemic hemodynamics, and showed a trend towards better clinical outcome and this is in agreement with the results of the present study. They recommended that the drug merits further evaluation with different dosages and longer schedules.

Testro et al., [24] reviewed outcomes of 69 patients treated with terlipressin between 2001 and 2005. Their findings showed that 49 episodes (71%) of HRS were type 1, and 20 episodes (29%) were type 2. Forty-one (59.4%) patients responded to terlipressin. However, they concluded that terlipressin is having better results in HRS type1 patients compared to HRS type 2 patients as patients survived; 17 (81%) had type 1 HRS while four (19%) had type 2 HRS. Therefore, they found it difficult to justify the use of this drug in patients with type 2 HRS who are not liver transplant candidates. Patients with type 1 HRS were not included in the present study; hence the results of the present study cannot verify the results obtained by Testro et al.

Conclusions

Terlipressin improves renal functions in patients with hepatorenal syndrome (type 2). The use of Terlipressin as a therapeutic option in patients with hepatorenal syndrome was not associated with significant short term adverse effects. Most of patients with type 2 hepatorenal syndrome have no identifiable precipitative factors.

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