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Efficacy of Terlipressin and Albumin in the Treatment of Hepatorenal Syndrome

Farukh Naz Silawat, Muhammed Khalid Shaikh, Raj Kumar Lohana, Bikha Ram Devrajani, Syed Zulfiquar Ali Shah and Asif Ansari

Department of Medicine, Liaquat University of Medical and Health Sciences Jamshoro, Sindh, Pakistan

Abstract: This Quasi experimental study was conducted to determine the efficacy of terlipressin and albumin in the treatment of hepatorenal syndrome on 60 patients of hepatorenal syndrome, who were admitted in medical wards of Liaquat University Hospital Hyderabad. The subjects were diagnosed as a hepatorenal syndrome on the basis of major criteria proposed by international ascites club, once diagnosis of HRS was made then patient was randomized into study / control group by random allocation and then treated accordingly with Terlipressin together with albumin and symptomatically, respectively. Sixty patients of HRS enrolled in the current study, out of these 30 were randomized in control group A, who were received placebo whereas another 30 patients were randomized in the study group B, which were treated by Terlipressin and albumin. After treatment marked reduction in serum creatinine was observed in Group B patients (3.01 ± 1.255 to 1.34 ± 0.554) as compared to group A (3.68 ± 1.69 to 3.89 ± 2.56) similarly creatinine clearance also significantly improved in Group B patients (29.60 ± 7.14 to 68.30 ± 28.35) than group A (26.4 ± 9.4 to 26.56 ± 9.39). According to results of current study in group B, 20 patients recovered (66.7%), 6 patients expired (20%) and 4 (13%) patients failed who recovered after 7 days treatment with Terlipressin and albumin. Whereas in group A, 10 were recovered (33.3%), 8 patients were expired (26.7%) and 12 patients (40%) failed to recovered after 7 days of symptomatic treatment. The self limiting side effects including Headach in 5 patients, crampy abdominal pain in 3 patients and digital ischemia was observed in only 1 patient. Terlipressin with albumin appears to be a safe and effective treatment of hepatorenal syndrome.

Key words: Albumin · Hepatorenal Syndrome · Terlipressin

INTRODUCTION

Hepatorenal syndrome is the development of functional renal failure in patients with advanced liver disease and portal hypertension, [1,2] in the setting of chronic hepatitis and acute hepatic failure [3].There are many options of treatment for hepatorenal syndrome, but the liver transplantation is the only curative treatment of hepatorenal syndrome, but this scenario has changed [4,5] with increased understanding of pathogenesis has led to successful attempts to reverse hepatorenal syndrome non-surgically with combination of systemic vaso constrictors and volume expanders [6], so in this way they not only serve as bridge to live transplantation, but they also improve survival in hepatorenal patients [7]. Among such, treatment with vasoconstrictor (Terlipressin) and plasma expansion with albumin is beneficial [7,8].

It was documented that efficacy of Terlipresin is more enhanced by combine administration of albumin in improving renal function as compared to Terlipressin alone. Parshant Solanki and his coworkers [9] performed clinical trail which indicates that Terlipersin significantly improved renal functions and systemic heamodynamics so it is quite beneficial in patients of hepatorenal syndrome with fewer side effects. In an another study, Colle and his co workers [10] proved that Terliprissin is most currently studied vasopressin analogue, the administration of Teripressin and albumin significantly improve glomerular filtration rate and increasing the arterial pressure and reduction in serum creatinine in 42 to 77% of cases.

Corresponding Author: Dr. Syed Zulfiquar Ali Shah, Department of Medicine, Liaquat University of Medical and Health Sciences Jamshoro, Sindh, Pakistan, Cell: +92-300-3057155, E-mail: zulfikar229@hotmail.com.

The rationale behind this study was to improve circulatory function by causing splanchnic vasoconstriction with Terlipressin, increase central blood volume thru albumin and then the beneficial effect of Terlipressin and albumin in hepatorenal syndrome was observed.

MATERIALS AND METHODS

The Quasi experimental study conducted on 60 patients of hepatorenal syndrome, who were admitted in medical wards of Liaquat University Hospital Hyderabad / Jamshoro, during six months study period (August 2009 to January 2010). The patients with acute / chronic liver disease chronic hepatitis and liver cirrhosis were admitted in the ward though emergency (ER). Once the diagnosis of hepatorenal syndrome established then he / she was randomized in control / study groups i.e. Group A and Group B, respectively. Random allocation was done by making 60 envelops, out of these, 30 was showing treatment with Terlipressin and albumin and represent study (Group B) while other 30 envelops were contained symptomatic treatment with fluid restriction, dopamine infusion, (renal dose) plasma expenders like Heamacceal / Gelafundin, antibiotics, which represent control group (Group A). Patient choose only one envelop and then he was treated accordingly.

The inclusion criteria of the study were age 18 years and above, acute/chronic liver disease, rapidly progressive reduction in renal function e.g. serum creatinine> 1.5-mg/dL, proteinuria, no evidence of granular cast in urine analysis or on ultrasonographic evidence of obstructive uropathy or parenchymal renal disease and no improvement in renal function after plasma volume expansion, while the exclusion criteria are ongoing shock, uncontrolled bacterial infection, current significant fluid losses, current/recent treatment with nephrotoxic drugs, severe cardiovascular disease and evidence of intrinsic/parenchymal renal disease.

The diagnosis of acute / chronic liver disease was confirmed by clinical, laboratory and radiological criteria, which include decreased live span / hepatomegaly, presence of ascites, spleenomegaly, spider nevi, gymecornatia low serum albumin, raised prothrombin, liver function test and ultrasound abdomen. On other hand,diagnosis of hepatorenal syndrome was made according to major and additional criteria proposed by international ascites club. The major criteria are necessary for diagnosis of hepatorenal syndrome and include: (1) Glomerular filtration rate as indicated by serum creatinine $\geq$ 1.5mg or 24 hours creatinine clearance <40ml / min (2) absence of shock, ongoing bacterial infection, fluid loses, current treatment with nephrotoxic drugs. (3) No sustained improvement in renal function following diuretic withdrawal and expansion of plasma volume with 1.5L of plasma expander. (4) Proteinuria less than 500 mg per dl and no ultrasonogrphic evidence of obstructed uropathy or parenchymal renal disease. Informed consent was obtained form all the subjects recruited regarding side effects of the drugs, benefits of the drug and the ratio between side effects and benefits. The dose of Terlipressin was 0.5-2mg/day with albumin in a dose of 12.5mg per day, efficacy was measured by reversal of HRS or improvement in renal function which was assessed by clinical as well as laboratory criteria which are given above and as well as number of side effects of Terlipressin and albumin like hypertension, abdominal pain, ischemia, cardiac arrhythmia was also assessed. Regarding ethical justification patients were treated free of cost.

The data were evaluated in statistical program SPSS version 11.0. Paired t-Test was applied for continuous variables and Pearson's chi square test was used for categorical parameters. P value < 0.05 was considered statistically significant.

RESULTS

Out of 60 patients, 30 patients randomized in group B were treated with Terlipressin and albumin infusion in a dose of 0.5 to 1 mg 12 hourly and 12.5 g /day, respectively. Whereas remaining 30 patients randomized as group A were treated symptomatically with dopamine infusion (4ug / min), plasma expander like Gelafundin, Haemacel and antibiotics

A remarkable improvement of renal function was observed in group B HRS patients who received Terlipressin and albumin, they showed marked increased in 24 hours urinary output and in serum creatinine clearance, similarly blood urea level also decreased and progressive decline in serum creatinine level also noticed in significant number of HRS patients in group B. According to the result of the current study no significant difference was observed in the base line clinical profile of patients in both groups. The effect of Terlipressin and albumin in patients with hepatorenal syndrome in relation to different parameters is mentioned in table 1.

Table 1: Effect of Terlipressin and Albumin in Patients with Hepatorenal Syndrome

	Group B patients (n = 30)		
Parameter	Baseline*n* = 30	After treatment*n* = 30	P - Value
Blood urea	96.0 ± 20.66	52.5 ± 15.39	< 0.001
Serum creatinine	3.01 ± 1.255	1.34 ± 0.554	< 0.001
Serum sodium	133.00 ± 4.267	134.53 ± 4.493	0.006
Serum potassium	4.69 ± 0.964	4.32 ± 0.474	0.006
24 hours urine volume	443.33 ± 127.882	1763.3 ± 470.86	<0.001
Creatinine clearance	29.600 ± 7.1467	68.300 ± 28.351	<0.001
Serum albumin	2.45 ± 0.673	2.77 ± 0.745	0.01
Serum Bilirubin	3.40 ± 2.092	3.37 ± 9.499	NS
Prothrombin time	29.46 ± 8.320	28.44 ± 9.499	NS
BP systolic	92.3 ± 19.77	97.0 ± 17.05	0.02
BP diastolic	55.3 ± 14.79	64.0 ± 10.20	0.002

Table 2:Terlipressin And Albumin Is More Effective Than Symptomatic Treatment (*N* = 60)

Outcome	Group A Symptomatic *n* = 30 (%)	Group B Terlipressin *n* = 30 (%)	P – Value
Expired	08 (26.7%)	06 (20.0%)	0.02*
Recovered	10 (33.3%)	20 (66.7%)	
Not recovered	12 (40.0%)	04 (13.3%)	

*P value is statistically significant

The base line renal function parameters did not differ significantly between two groups, but after treatment significant improvement in renal function were seen in patients receiving Terlipressin and albumin i.e. group B as compared to patients received symptomatic treatment i.e. group A. Improement in creatinine clearance noticed in group B (29.60 ± 7.14 to 68.30 ± 28.35 P < 0.001) as compared to group A (26.4 ± 9.4 to 26.56 ± 26.56 ± 9.39), serum creatinine declined in patients of group B after treatment with Terlipressin and albumin (3.01 ± 1.255 to 1.34 ± 0.554, P <0.001) than group A (3.68 ± 1.69 to 3.89 ± 2.56, P = non significant). The Terlipressin and albumin is more effective than symptomatic treatment as shown in table 2.

The urine output increased in both group A and B patients, but in group B, similarly after treatment blood urea level decreased more in group B patients (96 ± 20.6 to 52.5 ± 15.3, p <0.001) than group A (132.9 ± 43 to 127 ± 18.8, P = non significant). The blood pressure also improved in patients treated with Terlipressin and albumin. The serum albumin also improved in patients received Terlipressin and albumin infusion i.e. Group B (2.45 ± 0.67 to 2.77 ± 0.7, P = 0.01) than group A (1.98 ± 0.6 to 19.4 ± 0.5, P = non significant).

The Terlipressin treatment was associated with transient self limiting side effects including crampy abdominal pain in 3 patients, headache was noticed in 5 patients and digital ischemia was observed in only 1 patient.

DISCUSSION

Chronic liver disease is an extremely common in Pakistan due to extra ordinary increased incidence of hepatitis B and C virus infection, hepatorenal syndrome is a major complication in cirrhosis. It is the development of renal failure in the absence of clinical renal failure in the absence of clinical laboratory or histologic causes of renal dysfunction in patients with advanced chronic liver disease who has portal hyperteniosn and ascites.

Our results are in keeping with results of several recent trials using Terlipressin alone or Terlipressin and albumin together. Terlipressin has advantage our other vasopressin analogue (Octapressin, Ornipressin), of a longer biological half life (2-10 hours), allowing for intravenous bolus administration instead of continuous intravenous infusion. Hadengue *et al*. [11], in a double blind cross over study, found that Terlipressin given as 1mg 12 hourly for 48 hours improved diuresis, creatinine clearance and increased arterial pressure with negligible side effects in patients with HRS. Halimi *et al*.[12] observed a reduction in serum creatinine and improvement in urine output in subjects who received Terlipressin, 4mg/24 hours for 1 week. Similarly Uriz *et al*. [13] had shown that combination of Terlipressin and albumin infusion results in a significant reduction in the serum creatinine levels and improvement in the mean arterial pressure, GFR and the urine out put.

In the current study, 60 patients of chronic or acute liver disease were selected, who met the inclusion criteria of HRS and randomized into two groups A and B. Group A in present study received symptomatic treatment in form of dopamine infusion at renal dose (4µg / min), plasma expenders like Heamaccel and Gelafundin, as well as paracentesis, diuretics and antibiotics also given as symptomatic treatment whereas Group B patients were treated with Terlipressin and albumin. Our results identified that urine out put, blood pressure, blood urea, serum creatinine, creatinine clearance and serum albumin significantly improved in patients treated with Terlipressin and albumin. In the current study, the dose of Terlipressin was lower than that recommended for management of variceal bleeding because most patients included in the current study showed a positive response on 0.5 to 1mg 12 hourly so the incidence of side effect was noticed in only few patients which is most likely dose dependents and the duration of treatment is also variable and depends on the severity of HRS. Some patients recovered after 3 days of treatment while in others a more prolonged administration was required. In the current trial, the Terlipressin was given in combination with albumin infusion to further enhance the efficacy of Terliprssin, it is very unlikely that the beneficial effects of treatment was due exclusively to the administration of albumin, it alone has only minor or no effects on circulatory and renal function in patients with cirrhosis and renal dysfunction.

According to the present study, only three patients noticed crampy abdominal pain during Terlipressin therapy while 5 patients noticed headache and digital ischemia was observed in only one patient. These side effects were self limiting and did not require discontinuation of Terlipressin therapy. In group A HRS patients treatment modalities were other than Terlipressin and albumin and these were failed to improve renal function in significant number of patients and such observation is consistent with the study by Cardenas *et al* [14]. Therefore our study reinforced the previous observation of effectiveness of Terlipressin and albumin with reduction in adverse effects.

In conclusion, hepatorenal syndrome is a common complication in patients with acute or chronic live disease, the data collected through this randomized clinical trail indicate that Terlipressin together with albumin infusion is quite more beneficial in HRS patients with low incidence of side effects.

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