TERLIPRESSIN THERAPY RESPONSE ASSESSED BY COLOUR DOPPLER IMAGING IN PATIENTS OF HEPATORENAL SYNDROME

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ABSTRACT

BACKGROUND

The resistive index of renal arteries is the most widely used parameter to estimate the arteriolar vascular resistance in HRS. We aimed to evaluate the effects of terlipressin on renal haemodynamics using resistive index of renal interlobar arteries in such patients.

MATERIALS AND METHODS

An interventional randomised controlled clinical trial was planned with two groups, namely study group and control group. The study enrolled 40 cases of hepatorenal syndrome. These 40 cases were randomly allocated using computer generated random allocation sequence into two groups of size 20 each. The twenty patients of study group received terlipressin therapy, and other twenty comprised the control group. All underwent upper GI endoscopy and Colour Doppler examination. Terlipressin 1 mg 6 hourly intravenously was administered to patients in the study group for 2 days after which Doppler studies were repeated to evaluate the effect of terlipressin on resistive index.

Statistical Analysis- Statistical analysis included paired t test for intragroup comparison and unpaired t test for intergroup comparison. A 'p' value of <0.05 was considered statistically significant.

Settings and Design- The present study was carried out in Department of Medicine, Department of Radiology Department of Gastroenterology, SS Hospital, BHU Varanasi. A total of 40 cases of clinically suspected and diagnosed cases of hepatorenal syndrome on the basis of criteria defined by International Ascites Club Consensus Workshop in 2007 were taken, among them 20 patients in which terlipressin was used comprised the study group and 20 patients in which terlipressin was not used comprised the control group. Informed consent had been obtained from patients.

RESULTS

On examination, ascites was detected in all patients in both study and control groups. Majority of chronic liver diseases leading to HRS were related to alcohol followed by hepatitis B in both groups. There was significant reduction in mean resistive indices in interlobar arteries indicating beneficial effect of terlipressin on renal haemodynamics. There was significant decrease in resistive index of interlobar renal arteries in study group as compared to control group, after terlipressin therapy.

CONCLUSION

This study is first of its kind to utilise colour flow imaging for objective assessment of renal haemodynamics using resistive index as a parameter and study the favourable effect of Terlipressin in patients of hepatorenal syndrome.

KEYWORDS

Cirrhosis; Complications; Terlipressin; Ultrasound; Liver Failure; Hepatorenal Syndrome.

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BACKGROUND

Hepatorenal syndrome (HRS) is described as a "functional" and reversible form of renal failure that occurs in patients with advanced chronic liver disease. The distinctive hallmark feature of HRS is the intense renal vasoconstriction caused by interactions between systemic and portal haemodynamic.

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This results in activation of vasoconstrictors and suppression of vasodilators in the renal circulation. Renal failure is a common complication of cirrhosis and is a poor prognostic indicator.

The annual frequency of HRS in cirrhotic patients with ascites is roughly 8%, and in some reports as high as 40%.

Duplex Doppler ultrasonography of the kidneys is a safe easy and non-invasive method to assess blood flow and arterial vascular resistance as a parameter for vasoconstriction. The resistive index of renal arteries is the most widely used parameter to estimate the arteriolar vascular resistance and to evaluate renal haemodynamics. It is regularly used for screening of transplant rejection or to diagnose renal artery stenosis.

Since the main pathophysiology of HRS is splanchnic arterial vasodilatation and renal arterial vasoconstriction that

causes increase in resistive index (RI) of renal arterial system and the terlipressin (intravenously administered vasopressin 1 receptor agonist) causes selective vasoconstriction of splanchnic arterial vessels, which tends to reverse alterations in renal haemodynamic. In this study, we aim to evaluate effects of terlipressin on renal haemodynamics with the help of resistive index as an indicator of renal interlobar arteries in patients of hepatorenal syndrome.

MATERIALS AND METHODS

An interventional randomised controlled clinical trial was planned with two groups namely study group and control group.

Sample Size

Some prior studies have reported normal mean RI values of 0.64 ± 0.05 (21 patients), 0.58 ± 0.05 (109 kidneys) and 0.62 ± 0.04 (28 patients). In general, most sonographers now consider 0.70 to be the upper threshold of the normal RI in adults. Now considering a difference of 5% after treatment as compared to before treatment and assuming equal standard deviation of ± 0.05 for pre and post measurement and further, assuming a moderate coefficient of correlation of 0.60 between pre and post values, the sample size for each group would be 18 taking the level of significance as 5% and power as 90%. Now further, assuming 10% loss to follow-up the required sample size will now be 20 in each group.

Thus, the study enrolled 40 cases of hepatorenal syndrome. These 40 cases were randomly allocated using computer generated random allocation sequence into two groups of size 20 each. The twenty patients of study group received terlipressin therapy, and other twenty comprised the control group.

This study was carried out in the collaboration of three departments (Medicine, Radiology and Gastroenterology) of Sir SSL Hospital, Banaras Hindu University, and Varanasi, India during the period of January 2012 to June 2013. A thorough clinical and relevant laboratory evaluation had been performed for enrolment of patients to meet the criteria defined by International Ascites Club Consensus Workshop in 2007. A total of 40 cases of hepatorenal syndrome were enrolled, out them 20 patients received the terlipressin dose (study group) and remaining 20 patients did not receive terlipressin (control group). The study was approved by the review board and ethical committee of Institute of Medical Sciences, Banaras Hindu University, Varanasi. The study protocol conformed to the ethical guidelines of the 1975 Declaration of Helsinki (6th revision, 2008). Informed consent was obtained from the patients.

Radiological Evaluation for Resistive Index of Renal Interlobar Arteries

The patients were instructed to avoid oral intake at least 4 hours before procedure to reduce masking by gas. Patients were excluded if it was not possible to measure resistive index in two different places in each kidney due to massive ascites or masking by gaseous shadows. Colour Doppler examination and calculation of resistive index were performed using a Philips IU-22 ultrasound unit and a 3.5-5 MHz convex probe. Doppler signals were obtained from interlobar arteries along the border of medullary pyramids. These consecutive measurements at the upper middle and lower pole of the organ

were averaged, at the same time bipolar length of kidney, s/o kidney size and cortical thickness were also measured. All Doppler examinations were done by single examiner having experience of more than 10 years who was blinded to results of haemodynamic measurement. Resistive index had been determined before and two days after terlipressin therapy.

Terlipressin Therapy

After baseline radiological evaluation, Terlipressin 1 mg 6 hourly intravenously had been administered to patients in the study group for 2 days after which follow-up radiological evaluation had been done by recalculating the resistive index in the interlobar arteries and evaluating the effect of terlipressin on resistive index.

Statistical Analysis

All values were expressed as Mean $\pm$ SD. Statistical analysis included paired t test for within the group comparison and unpaired t test for between the group comparisons. For basic characteristics and various sign and symptoms, number and percentage were calculated and Chi square test was applied for inter-group comparison of these variables. A 'p' value of < 0.05 was considered statistically significant.

RESULTS

The mean age of presentation was 54 years in both study group and controls. In both groups, male population dominated over female. Males constituted 85% and 90% in study group and controls respectively without any statistically significant difference ($\chi^2 = 0.334^a$, $p = 0.846$). In the study group, all patients presented with abdominal distension (100%), decreased urinary output (100%) and jaundice (100%) followed by melaena (65%), altered sensorium (55%) and hematemesis (45%). In the control group, abdominal distension, jaundice and decreased urinary output were universal presenting complaints followed by melaena, haematemesis and altered sensorium (70%, 40% and 30% of patients respectively).

On ultrasound examination, ascites was detected in all patients both in study and control groups. Splenomegaly was observed in 90% in the study group and 80% of the control group and hepatomegaly was detected in 45% of the study group and 70% of the control group.

Majority of chronic liver disease leading to HRS were related to alcohol in both the groups (50% vs. 45%) followed by hepatitis B (20%) in both groups. In the control group, 15% were related to Hepatitis C virus as opposed to 10% in the study group. Cause could not be found in 15% of the study group while this number was lower in the control group (10%). No patient of autoimmune liver disease could be found in this study in any of the two groups. Wilson disease was the cause of chronic liver disease in 5% in the study group and 10% in the control group.

Resistive Index Analysis

The baseline value of mean resistive index value of right and left kidney in upper middle and lower interlobar renal arteries was calculated in both groups (Table 1). In study group, this value for upper middle and lower interlobar arteries were 0.7270 ± 0.03935 , 0.7170 ± 0.03262 , 0.6995 ± 0.05021 respectively while in control group this value for upper middle and lower interlobar arteries were 0.69820 ± 0.01473 , 0.6960

± 0.01635 , 0.7225 ± 0.01482 respectively. After administration of terlipressin, resistive index was calculated in the study group (Table 2) and compared with the resistive index of control group (Table 3). The values clearly demonstrate significant reduction in mean resistive indices in all upper, middle and lower interlobar renal arteries which is indicative of significant and beneficial effect of terlipressin on renal haemodynamics in the form of reduction in resistive indices of renal interlobar arteries.

Variables	Study Group (n = 20) RI Mean $\pm$ SD	Control Group (n = 20) RI Mean $\pm$ SD	p-value
Interlobar arteries (R+L) Upper	0.7270 $\pm$ 0.03935	0.69820 $\pm$ 0.01473	0.004
Interlobar arteries (R+L) Middle	0.7170 $\pm$ 0.03262	0.6960 $\pm$ 0.01635	0.014
Interlobar arteries (R+L) Lower	0.6995 $\pm$ 0.05021	0.7225 $\pm$ 0.01482	0.057

Table 1. Baseline Resistive Index in Interlobar Arteries in both Groups

Variables	Pretreatment RI value (Study Group) Mean $\pm$ SD	Post treatment RI value (Study Group) Mean $\pm$ SD	p-value
Interlobar arteries (R+L) Upper	0.727 $\pm$ 0.03935	0.6275 $\pm$ 0.0477796	<0.001
Interlobar arteries (R+L) Middle	0.717 $\pm$ 0.032620	0.6415 $\pm$ 0.0464843	<0.001
Interlobar arteries (R+L) Lower	0.6995 $\pm$ 0.05021	0.6340 $\pm$ 0.04333	<0.001

Table 2. Effect of Terlipressin on Resistive Index of Interlobar Arteries in Study Group

Variables	R.I. Pre (Control Group) Mean $\pm$ SD	R.I. Post (Control Group) Mean $\pm$ SD	p-value
Interlobar arteries(R+L) upper	0.6980 $\pm$ 0.01473	0.6990 $\pm$ 0.01372	0.541
Interlobar arteries (R+L) middle	0.6960 $\pm$ 0.01635	0.69600 $\pm$ 0.01060	1.000
Interlobar arteries (R+L) lower	0.7225 $\pm$ 0.01482	0.7195 $\pm$ 0.01959	0.163

Table 3. Resistive Index in Control Group who did not Receive Terlipressin Therapy

DISCUSSION

Hepatorenal syndrome (HRS) is a reversible form of functional renal failure that occurs predominantly with advanced liver disease and fulminant liver failure.^[1] Despite advancing research in HRS, its aetiology and medical therapy has not been fully resolved. HRS encompasses 2 distinct types. Type 1 HRS often manifests itself rapidly; without appropriate treatment the mean survival time is approximately 2 weeks.^[2] The core feature of pathogenesis of HRS is peripheral arterial vasodilatation, particularly in the splanchnic vasculature.^[3,4] This develops with advanced liver cirrhosis, which causes

increased resistance to blood flow with high portal pressure. In turn, to reduce the pressure within the hepatic portal system, locally acting vasoactive substances are released that cause vasodilatation of the splanchnic vasculature.^[5] These compensatory mechanisms with time become detrimental and result in sustained severe intrarenal arterial vasoconstriction with progressive physiological renal failure. The pooling of blood in the splanchnic vascular bed with the associated hypoperfusion of the kidneys and the ensuing intrarenal arterial vasoconstriction forms the basis for the development of HRS. In the present study, majority of patients were alcohol related in both groups (50% vs. 45%) followed by hepatitis B (20% each) related in both the groups. (Table 2) Thomas R Frieden et al in his study found the aetiology of CLD as follows: both alcohol and hepatitis C infection (46%); alcohol abuse alone, (29%); HCV related alone (12%); both alcohol abuse and chronic hepatitis B virus infection (6%).^[6] Mendez Sanchez in his study found the various aetiologies of liver cirrhosis as follows: alcohol 39.5%, HCV 36.6%, cryptogenic 10.4%, HBV in 5%.^[7] In a study done by Hsu YN et al in elderly Asian population, it was found that 44.9% had chronic hepatitis C and 19% had had chronic hepatitis B.^[8] In a study done in Maharashtra by Amrapurakar et al, he found following aetiologies: HBV related 40.5%, alcohol related 39% and HCV related 17% and rest (3.5%) to be cryptogenic which is very similar to our results.^[9] Duplex ultrasonography is a widely used safe non-invasive method to assess vascular patency and blood flow in many sites. Duplex Doppler can be used to assess vascular resistance in the small intraparenchymal vessels through simple analysis of Doppler waveform by a parameter termed the resistive index (RI). An elevated renal RI has been observed in various conditions associated with elevated renal vascular resistance such as kidney obstruction, acute tubular necrosis and haemolytic uremic syndrome and should be detected in liver disease related functional kidney failure. Previous data show that RI values decrease from renal hilum to the cortex. RI values measured in the interlobar-arcuate arteries are expected to show the most consistent results. The correlation between increased RI and azotaemia seems to confirm the role of vasoconstriction in the pathogenesis of cirrhotic kidney disease. Doppler ultrasound measurement of the RI is a useful index to quantify renovascular resistance in cirrhotic patients before HRS develops. HRS has very poor prognosis with spontaneous recovery being unlikely.^[10] Treatment of HRS can be divided into medical and surgical. The rationale of the use of vasoconstrictors in the treatment of type 1 HRS is to counteract the splanchnic arterial vasodilation in order to improve effective circulating volume and reduce portal pressure. Among vasoconstrictors, to this day, terlipressin is the most widely used in the treatment of type 1 HRS.^[11] In most studies, terlipressin has been used together with albumin starting with a priming dose of 1 g/kg BW followed by 20–40 g/day, monitoring central venous pressure. In two studies in which terlipressin was given also alone, reversal of renal failure was lower than in the studies in which terlipressin was associated with albumin.^[12] In this study, we found a significant increase in the renal resistive index of interlobar arteries among both groups. Maroto et al demonstrated that RI is significantly higher in decompensated cirrhotic patients with ascites than in compensated cirrhotic patients and that the RI of compensated cirrhotic patients is higher than in the controls. The relative risk of developing HRS

in patients with an RI = 0.70 was high. RI is a useful indicator in patients with cirrhosis and ascites for the diagnosis and prognosis of HRS.^[13] In Italy, Sacerdoti et al reported that the Pulsatile Index and Resistive Index were significantly higher in non-ascitic cirrhotic patients than in control patients. The Pulsatile Index and Resistive Index were significantly higher in Child-Turcotte-Pugh class B and C patients than in class A patients. This non-invasive method may be applied to pathophysiological and clinical studies of the renal functional impairment in cirrhosis.^[14] Hadengue et al carried out a double-blind, crossover, randomised study in 9 patients with type 1 HRS. The patients received terlipressin (2 mg/days for 2 days) and a placebo for 2 days in a randomised order. Terlipressin administration significantly increased creatinine clearance and urine output, but did not significantly change urinary sodium concentration. Urinary sodium excretion was not significantly different after placebo administration or terlipressin administration.^[15] The study by Solanki et al was a randomised, controlled, single-blind trial. They assigned 24 consecutive patients with HRS to treatment with terlipressin 1 mg IV at 12-hour intervals (group A, n = 12) or placebo at 12-hour intervals (group B, n = 12). The end-point of the study was improvement in renal function defined as reversal of HRS and survival at 15 days. Terlipressin administration was shown to be associated with an improvement in parameters of renal function, mean arterial blood pressure and importantly reversal of HRS in 5 of 12 patients of group A.^[16] Robertson M et al^[17] reviewed outcomes of 69 patients treated with terlipressin between 2001 and 2005. Forty-one (59.4%) patients responded to terlipressin. Twenty-one (30.4%) patients survived; 17 (81%) had type 1 HRS while 4 (19%) had type 2 HRS (P = 0.27). Terlipressin associated with albumin therapy was associated with marked improvement in renal function, reversal of HRS and improvement in circulatory function with an increase in mean arterial blood pressure.^[18-20] Several meta-analyses have been conducted to determine the effect of terlipressin in HRS with regard to the duration of treatment.^[21,22] Fabrizi et al^[23,24] showed in their meta-analysis that discontinuation of terlipressin therapy was associated with a significant increase in the number of relapses. Furthermore, terlipressin was more effective in reversing HRS than placebo without apparent impact of terlipressin on survival in HRS patients. This may again suggest the need for large clinical trials addressing the impact of terlipressin in HRS patient survival. Interestingly, administration of albumin with terlipressin showed a reduction in mortality in type 1 HRS. Therefore, the current evidence from abovementioned trials suggests that terlipressin can have a potential benefit in treating HRS and that an improvement in survival. Terlipressin has few adverse side effects, which allows patients to continue with treatment in order to achieve desirable effects.

CONCLUSION

In our study, we evaluated the effect of terlipressin therapy on renal haemodynamics in patients of hepatorenal syndrome which showed significant decrease in resistive indices of renal interlobar arteries. Hence, we conclude that terlipressin causes significant decrease in renal vasoconstriction, which is a key feature in pathophysiology of renal injury observed in patients of hepatorenal syndrome, and therefore, terlipressin

based therapy is the sheet anchor in medical management of hepatorenal syndrome.

There was significant decrease in resistive index of interlobar renal arteries in study group as compared to control group, after terlipressin therapy, confirming previous studies and indicating the fact that terlipressin causes significant reduction in renal vasoconstriction as reflected by decrease in resistive indices of interlobar renal arteries.

There was no significant change in cortical thickness of kidney in both groups elaborating the fact that this parameter is indicative of chronic disease process and not altered by short-term terlipressin therapy.

This study is first of its kind to utilise colour flow imaging for objective assessment of renal haemodynamics using resistive index as a parameter and study favourable effect of Terlipressin in patients of hepatorenal syndrome.

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