Original Research Paper

Volume-7 | Issue-11 | November-2017 | ISSN - 2249-555X | IF : 4.894 | IC Value : 79.96

Gastroenterology

PREDICTORS OF RESPONSE TO TERLIPRESSIN PLUS ALBUMIN THERAPY IN HEPATORENAL SYNDROME (HRS) TYPE 1

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ABSTRACT

BACKGROUND AND AIM : Hepatorenal syndrome type1 (HRS1) is rapidly progressive form of renal failure occurring in cirrhosis. Terlipressin plus albumin is effective in reversing type 1 HRS .Since 1/3 to 1/2 of patients respond to treatment , predictors of response and survival would help identify the patients likely to benefit from treatment .Aim of the study was to find predictors of response to terlipressin plus albumin therapy in HRS1 and survival at 1 month and 3 months.

METHODS : 64 adult patients with HRS1 from June 2013 –June 2016 included in this study. Patients were treated with terlipressin 1mg IV 6 hourly and IV albumin until creatinine <1.5 or develops complication /death/maximum upto 14 days. Primary outcome was reversal of HRS or death and secondary outcome was recurrence of HRS , side effects, transplant free survival at 30 and 90 days.

RESULTS : Of 64 patients 58 were treated with TAT . 34 patients (58.2%) recovered,24 patients (41.38%) not responded. Baseline s. creatinine was predictive of response to treatment (2.88±0.4 Vs 3.95± 1.2),P value 0.025. ROC curve with s.creatinine level of 3.25 was associated with sensitivity of 75 % , specificity of 85.7% . There was significant difference in the mean survival of responders and non responders (52 days Vs 7 days)

CONCLUSIONS : Baseline s.creatinine significantly correlates with HRS treatment response and there was significant difference in the mean survival of responders and non responders .

KEYWORDS : Hepatorenal syndrome type1 (HRS1), cirrhosis, terlipressin, s.creatinine

INTRODUCTION

Hepatorenal syndrome (HRS) is a rapidly progressive but potentially reversible form of prerenal failure that happens in patients with cirrhosis and ascites .It is associated with high morbidity and mortality. The incidence of HRS in patients with cirrhosis and ascites is 18% after 1 year, and increases to 39% after 5 years.(1) The main pathophysiological basis for the development of HRS is the progressive systemic arterial vasodilatation, especially in the splanchnic bed ,which leads to reduction in effective arterial blood volume with subsequent activation of renal sodium-retentive mechanisms and intrarenal arterial vasoconstriction (4) leading to renal failure in the absence of intrinsic kidney disease.The median survival of type-1 HRS averages 2 weeks and that of type 2 HRS is 4-6 months. As a first-line therapy of type 1 HRS, both the International Ascites Club (IAC) and the American Association for the Study of Liver Diseases (AASLD) recommend a combination of vasoconstrictors and albumin infusion [10]. The additive effects provided by vasoconstrictors and albumin infusion are thought to improve outcomes vs monotherapy with either agent. The vasopressors shown to be effective have been primarily either terlipressin, a vasopressin analogue, or the α-agonist midodrine combined with octreotide. Terlipressin (triglycyl-lysine-vasopressin), a synthetic vasopressin analog, acts via the vasopressin V1 receptor as a systemic vasoconstrictor and increases effective arterial volume and renal blood flow, thereby improving renal function in patients with HRS. Administration of terlipressin plus albumin is effective in reversing type 1 HRS(2,3) .However, only about 1/3 of patients respond to treatment, therefore, predictors of response and survival would help to identify the patients most likely to benefit from treatment. Infusions of vasopressin and its analog are associated with severe ischemic complications. The risk of unnecessary exposure to terlipressin in patients unlikely to respond may also be mitigated by stopping treatment at day 4 in those whose s.creatinine has not begun to decrease.(1) Although the most important aim of treating patients with type-1 HRS with vasoconstrictors and albumin is that of bridging these patients towards OLT, it is evident that such treatment should also be tested in non-transplant candidates, with the aim of prolonging survival, since in some patients possible survival benefits are far from trivial(9).

AIMS AND OBJECTIVES

1) To find the outcome of HRS patients treated with albumin terlipressin therapy (TAT) in a tertiary care centre.
2) To analyse various factors affecting response to treatment and patient survival in HRS.

METHODS

64 consecutive patients with HRS Type 1 from June 2013 -January 2016 admitted in Gastroenterology department, Medical college,Trivandrum included in this study.

Inclusion criteria: Adult subjects with acute or chronic liver disease and HRS type 1, as defined by the International Ascites Club criteria (serum creatinine >1.5 mg/ dl and no improvement in serum creatinine after at least 2 days with diuretic withdrawal and volume expansion with albumin} are included as cases.

Exclusion criteria

1) Evidence of parenchymal renal disease (eg, acute tubular necrosis, glomerular diseases, interstitial nephritis)or obstructive renal disease (urinary obstruction)
2) factors that would affect renal function independent of HRS (use of nephrotoxic drugs, shock, uncontrolled bacterial infection,uncorrected fluid losses, acute liver disease because of factors known to also be nephrotoxic), and
3) The presence of severe cardiovascular disease as determined by the clinical judgment.

Method: Detailed history (regarding etiology of cirrhosis,duration of ascites , recent alcohol intake ,recent LVP ,diuretic intake, precipitating factor of HRS like GI bleed, any infection,alcoholic hepatitis), clinical examination including blood pressure and urine output monitoring, and laboratory investigations – haemogram , Urine routine ,urine culture and sensitivity, urine sodium ,Renal Funcion Test ,Liver function test ,S.electrolytes ,chest X ray, USG abdomen,blood and ascitic fluid culture are recorded.

Patients are treated with terlipressin at a dose of 1 mg IV every 6 hourly and IV albumin 1gm/kg on day1 followed by 20-40 gm /day .Dose of terlipressin is increased to a maximum of 2 mg/4–6 h if there is no reduction in serum creatinine of at least 25% compared to the baseline value at day 3 of therapy. Treatment is maintained until serum creatinine has decreased below 1.5 mg/dl or the patient develops intolerable complications or death. Serum electrolytes, BUN, and creatinine were evaluated daily during treatment .

Outcome measures: The primary outcome is the reversal of HRS, defined as a reduction of serum creatinine to a value of <1.5 mg/dL during treatment. Secondary outcome measures are: Incidence of side-effects, death during treatment. Recurrence of HRS defined as Increase in serum creatinine >1.5 mg/dL in patients with complete response to treatment .Transplant free survival in patients treated with terlipressin ,evaluated at 30 days and 180 days. Patients are divided into two groups –Those responded to therapy and those who did not respond to therapy. Various factors effecting the response and survival between the groups are analysed.

Statistical analysis: Basic descriptive statistics like means, ranges and percentages, were used to characterize the populations. Statistical analyses included Student *t* tests for parametric data, and the Chi-Square Tests for nonparametric data. Variables which showed significance in univariate analysis are included in the multivariable logistic regression analysis and expressed as Odds Ratio(OR). Survival analysis done using Kaplan Mayer curve and compared using Log Rank test. Two-tailed P values less than 0.05 were considered statistically significant.

RESULTS

Of 64 patients with HRS , 58 were treated with TAT. All were males. Mean age was 52. Main precipitating factors of HRS were SBP, alcoholic hepatitis and cellulitis as shown in Table 1 . Of the 58 patients 34 patients (58.62%) recovered from HRS(Figure1) . 55% responded within 5 days of therapy . 24 patients (41.38%) not responded (2 completed therapy,14 withdrawn treatment due to adverse effects,8 expired during therapy) (Figure2). Abdominal pain was main cause for discontinuation of therapy. Of the responders 78.9% survived at 1 month and 15.7% at 3months. HRS recurred in 8 patients. 8 patients lost to follow up. Baseline serum creatinine was predictive of response to treatment (2.88±0.4 Vs 3.95± 1.2),P value 0.025. ROC curve with s.creatinine level of 3.25 was associated with sensitivity of 75 % , specificity of 85.7% and area under ROC of 0.839. There was significant difference in the mean survival of responders and non responders (52 days Vs 7 days.)(Figure3) . Kaplan Meier Log Rank test showed p value of 0.020. MELD score showed a significant difference for 3 months survival 20.5 ±3.7 Vs 30.4± 6.9 (P 0.015).

Table 1. Summary of Baseline Characteristics

	Responded	Not responded	P value
Alc hepatitis	20.8%	25.0 %	0.77
SBP	16.6%	29.66%	0.134
Cellulitis	16.66 %	20.06 %	0.766
Bilirubin	6.72 ± 8.23	9.33 ±9. 68	0.403
Albumin	2.55± 0.67	2.59 ±0.6 1	0.163
INR	1.90 ± 0.47	1.92 ± 0.62	0.925
S.Cr	2.88 ± 3.04	3.95 ± 1.05	0.025
S.Na	120.5± 7.3	128.75 ± 5.2	0.922
Platelet	1.24 ± o.61	1.20 ± 0.36	0.827

Figure 1. Treatment Outcomes

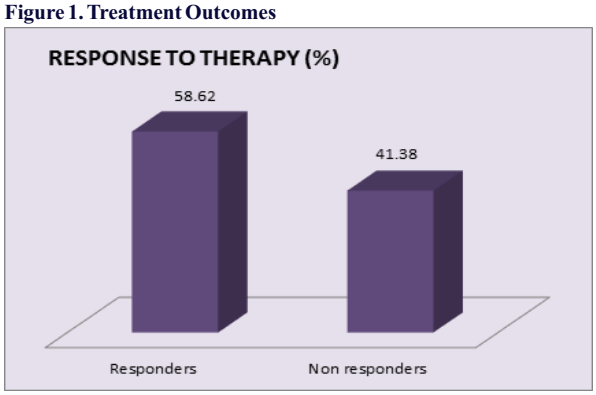


Figure2. Characteristics of non responders

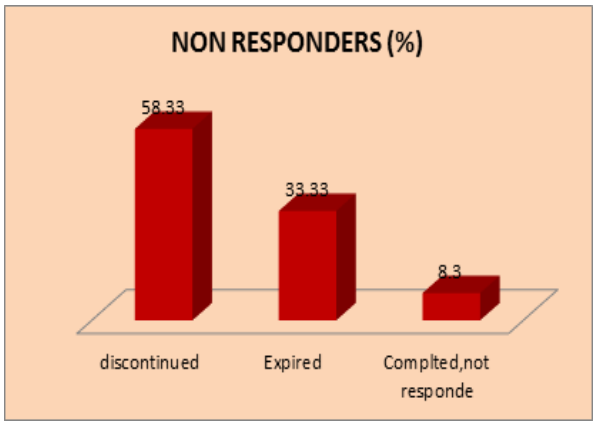
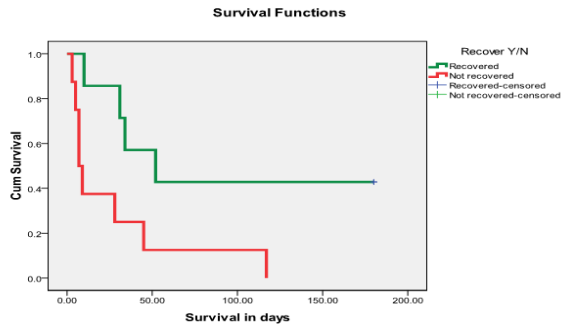


Figure 3.Survival characteristics of responders and non responders



DISCUSSION

The treatment for type 1 HRS patients has improved significantly with pharmacological treatment using vasoconstrictors and albumin in the last decade.(9) This treatment has provided for many patients a successful bridge to liver transplantation, the only definitive treatment for HRS [5]. The goal is to reverse in a very short time span the kidney failure before it leads to irreversible structural renal damage and death. However, only approximately 40 to 60 % of patients respond to the combination therapy with reversal of kidney failure [6,11,12]. In our study out of the 58 patients treated ,34 patients (58.62%) recovered from HRS. This efficacy rate is similar to that reported in a recent meta-analyses (13). In this study out of the 58 patients 24 patients (41.38%) not responded .Reasons for the lack of response are unknown but may include elevated levels of vasodilator cytokines, increased bacterial products or latent infections, and presence of concomitant adrenal insufficiency. These possible causes warrants investigation in order to improve the efficacy of treatment .Therefore, ways to improve the efficacy of the current treatment and to identify predictors of response are now interesting areas of research. [7,8]. Predictive factors of response reported in previous studies in patients with HRS included baseline Child- Pugh and MELD scores, serum creatinine, and arterial pressure . The only variable predictive of HRS reversal in our study was the baseline serum creatinine. The patient who is most likely to benefit from treatment with terlipressin and albumin is the one with early onset moderate renal failure (SCr <3.25 mg/dl) associated with sensitivity of 75 % , specificity of 85.7%. As the renal function worsens their likelihood of reversal of HRS with terlipressin and albumin declines . Based on this and previous studies, it would appear that baseline serum creatinine is consistently the best predictor of HRS reversal. The results of this study confirm data from previous studies indicating that patients with type 1 HRS who respond to treatment with terlipressin and albumin therapy have longer survival compared with that of nonresponders.(14,15) . In fact, in the current study, there was significant difference in the mean survival of responders and non responders (52 days Vs 7 days). Pharmacologic therapy with vasoconstrictors and albumin reverse HRS mainly by working on the splanchnic vasculature to redistribute part of the splanchnic blood volume back to the systemic circulation. Patients in our study could not undergo liver transplantation, although other studies showed that some of the patients underwent transplantation. These data, together with the observation that patients with HRS in whom renal function improves with terlipressin and albumin have an excellent post transplantation outcome similar to that of patients without HRS,(16) suggest that terlipressin plus albumin is an effective therapeutic option for patients with HRS awaiting liver transplantation.. Thus, in patients with type 1 HRS, terlipressin-induced improved renal function may have a beneficial effect on survival independently of the severity of the underlying liver disease. In our study, 14 patients withdrawn treatment due to adverse effects (mainly abdominal pain 60%).Terlipressin has been reported to have a lower incidence of ischemic complications compared with other vasopressin analogues (17). Ischemic adverse events were not observed in our study.

One limitation of our study was the small number of patients studied. So a study with larger number of patients will be useful for providing a better understanding of the effects of terlipressin and albumin in cirrhotic patients with HRS.

CONCLUSIONS

Treatment with terlipressin and albumin improves renal function in patients with cirrhosis and HRS. Baseline s.creatinine significantly correlates with HRS treatment response.However, the survival of cirrhotic patients with type 1 HRS remains poor, it may be improved by this pharmacological treatment using vasoconstrictors and albumin., Future research on management of type 1HRS should be needed to explore mechanisms of impaired response to pharmacological therapy and for implementation of new therapies for nonresponders.

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