

RRI as Diagnostic and Follow up Indicator in Cirrhosis of the Liver with Hepatorenal Syndrome and Refractory Ascites

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Abstract

Introduction: Hepatorenal syndrome (HRS) is a syndrome of functional renal failure occurring in patients with advanced liver failure in the absence of clinical, laboratory, or histological evidence of other known causes of renal failure. However HRS has always been considered to be potentially reversible. RRI (Renal Resistive Index) is an affordable, non invasive and easily available tool which can be used to detect the early onset of HRS. Large volume paracentesis and albumin infusion along with splanchnic vasoconstrictors are the mainstay in the treatment of refractory ascites. The cost of treatment with terlipresin is prohibitive for people in the rural areas but not so with noradrenaline. Therefore, noradrenaline should be an acceptable alternative, in a developing country, especially in Rural India.

Aim: The aims of this study were to determine the usefulness of RRI in diagnosis and follow up of HRS and to determine if large volume paracentesis with noradrenaline and albumin infusion can prevent patients from going into Hepatorenal syndrome.

Materials and Methods

- Type of study: Prospective Observational clinical study. Dept. Of Medicine MVJ MCand RH Hoskote.
- Patients with cirrhosis of liver, refractory ascites and an RRI of > 0.70 were included in the study.
- A protocol for LVP (Large volume paracentesis) was laid down and followed in each case. Follow up RRI was done on 2nd day, 7th day and after two months.

Results: 184 patients with cirrhosis of liver with tense ascites underwent RRI by USG Doppler. 53 patients with RRI of > 0.7 were included in the study, after fulfilling the inclusion and exclusion criteria of which 25 patients (Cases) gave informed consent; the remaining 28 who were not willing for LVP were considered as "controls". The mean RRI of cases was 0.7617±0.0457; the follow up mean RRI of cases on the 2nd day, 7th day and after 2 months were 0.6821±0.0466, 0.6375±0.0311 and 0.6030±0.0461 respectively, with the p value of 0.00001. In the control group the mean RRI was 0.7245±0.0174 and the follow up mean RRI on the 2nd day, 7th day and after 2 months were 0.7245±0.0174, 0.7191±0.0148 and 0.7368±0.01944 respectively, with the p value of 0.2100.

Conclusion

- RRI is an affordable, non invasive and easily available tool which can be included as part of a routine Ultrasonographic evaluation in liver cirrhotics. The RRI can be used for assessing early onset of HRS and in follow up.
- Large volume paracentesis, Noradrenaline with Albumin infusion (5 gms/litre of ascitic fluid removed) is as effective as other costlier options for refractory ascitis.

failure in a patient with liver disease and is a common complication of advanced cirrhosis.¹ The pathogenesis of HRS is renal vasoconstriction. The intra renal arterial doppler is a non-invasive tool used to study the extent of this vasoconstriction and the RRI is derived from it.² Large volume paracentesis is the first-line therapy for refractory ascites in patients with cirrhosis¹ and it has shown to be as effective as standard therapy.³ Paracentesis-induced circulatory dysfunction (PICD) is a disorder characterized by marked activation of the renin-angiotensin axis secondary to the further increase of an already established splanchnic arteriolar vasodilatation,¹ PICD is a frequent and potentially harmful complication of large volume paracentesis.³ In several studies^{4,5} Albumin is the most commonly used plasma expander; its safety and efficacy in preventing PICD is well demonstrated. In addition vasoconstrictor agents like noradrenalin (0.1-0.7mg/h) have also shown to reduce the incidence of PICD and preventing patients going into HRS. A combination of noradrenaline and albumin infusion has also been tried in order to increase glomerular filtration rate and renal plasma flow^{4,5} thereby improving the renal function and reversing the HRS.

In an earlier study done by Moshin et al⁶ it was seen that patients with RI ≥0.77 had massive ascites when compared to patients with RRI <0.77 and this was statistically significant (P = 0.02). This finding confirmed that elevated RRI is seen in patients who have worsened in their disease. These findings were observed in other studies done earlier by Götzberger et al⁷ (0.74 vs. 0.67, P < 0.01), Celebiet al⁸ and Rivolta et al.⁹

Introduction

Hepatorenal syndrome (HRS) is defined as an unexplained kidney

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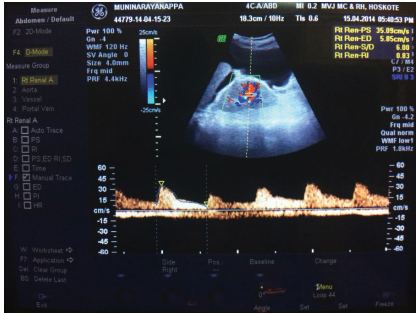


Fig. 1: Doppler picture of renal artery of the right kidney. Arrows pointing to peak systolic velocity and end diastolic velocity. Rt Ren-Ri calculated in right top corner (0.83)

A study conducted by Goyal et al¹⁰ revealed that patients with cirrhosis and ascites showed significantly increased RRI (0.72 ± 0.02) when compared to cirrhosis without ascites (0.62 ± 0.06). Elevated RRI >0.70 was present in 16% (8/50) patients in the group with cirrhosis alone and in 60% (30/50) patients in the group who had cirrhosis and ascites.

In this study we used LVP, Noradrenaline and Albumin for the treatment of HRS while monitoring with the RRI. We believe that this is the first study in INDIA using RRI as a criteria for diagnosis and follow up.

Aim of the Study

1. To determine usefulness of RRI in diagnosis and follow up of HRS.
2. To determine if large volume paracentesis, noradrenaline and albumin infusion can prevent patients from going into Hepatorenal syndrome.

Materials and Methods

This study was a descriptive observational prospective study and conducted in MVJ Medical College and Hospital Hoskote Bangalore in the year 2014-16 (over a period of two year). The Study was approved by the Institution's Research and Ethical Committee Board and informed consent for the trial was obtained from each person. The inclusion criteria were Patients > 18 years diagnosed to have cirrhosis of liver with refractory ascites clinically and sonologically. RRI >0.7 was also taken as inclusion criteria.

Duplex Doppler evaluation of the renal arteries was done using a 3.5-MHz convex transducer (GE Voluson 730 Pro).

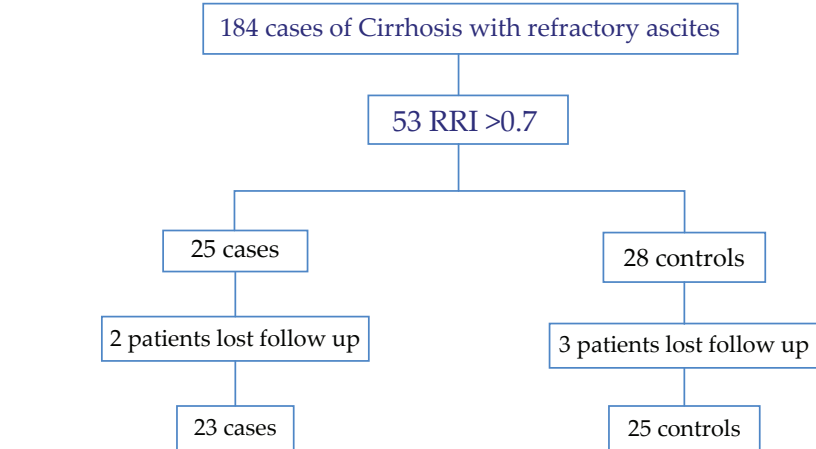


Fig. 2: Flow chart showing cases and controls

The patients were asked to fast at least 4 h before examination to reduce masking by intestinal gas. Doppler signals were taken from interlobar arteries and arcuate arteries in both kidneys. Colour doppler ultrasound was used to help to identify the arteries. A train of at least three similar, sequential time-velocity waveforms of Doppler signals was obtained at each point of measurement during suspended respiration. The RI was calculated with the formula $RI = (\text{peak systolic velocity} - \text{end diastolic velocity}) / \text{peak systolic velocity}$ (Figure 1). Patients were excluded if it was not possible to measure the RI in two different places in each kidney due to massive ascites or masking by gas. Inter-observer variability was kept to the minimum by having the same ultrasonologist perform the Doppler studies and patients with RRI >0.7 were included in the study.

The exclusion criteria were patients with other acute infections and potentially or overt cardiovascular instability, Diabetes mellitus, Hypertension, Suspected or overt malignant disease, Patients with nephropathies, or with pathomorphological findings in ultrasound like decreased kidney size, reduction of renal parenchymal width and significant renal parenchymal hyperechogenicity, Peripheral vascular thrombosis, mesenteric vascular thrombosis, hypersensitivity to adrenaline, Hypotension (systolic BP <90 mm Hg) and INR >2 after repeated correction with FFP.

Protocol for LVP Using Nor-Adrenaline

Large volume paracentesis (4 lit) was done over a period of 1 to 2 hrs. Albumin (5g/L) was given i.v. Noradrenalin

infusion rate was adjusted to keep the systolic blood pressure around 110 mmHg for a period of 24 hrs.⁵ Patient's vital signs were monitored in the ICU for 24 hours and Patients were instructed not to get up from the bed for 24 hours. Post paracentesis RRI was measured on day 2, day 7, and after 2 months.

The data was systematically collected, compiled and statistically analysed using IBM SPSS 22.0 Software to draw cross-tabs and make relevant conclusions. Differences between groups were analyzed by students t test and $p < 0.05$ was considered significant.

Results

For the purpose of making comparisons, the study population was divided into two groups of cases and controls. 184 patients with cirrhosis of liver with tense ascites underwent RRI by USG Doppler. 53 patients with RRI of > 0.7 were included in the study. After fulfilling the inclusion and exclusion criteria of which 25 patients (Cases) gave informed consent; the remaining 28 who did not consent for LVP, were considered as controls (Fig 2). While both cases and controls received standard treatment (diuretics, aldosterone antagonists and salt restriction) for cirrhosis of liver with ascitis, only cases received LVP along with noradrenaline and albumin infusion. In our study 84% of the patients were males of the age group 30-50 years.

The mean RRI of cases was 0.7617 ± 0.0457 ; the follow up mean RRI of cases on the 2nd day, 7th day and after 2 months were 0.6821 ± 0.0466 , 0.6375 ± 0.0311 and 0.6030 ± 0.0461

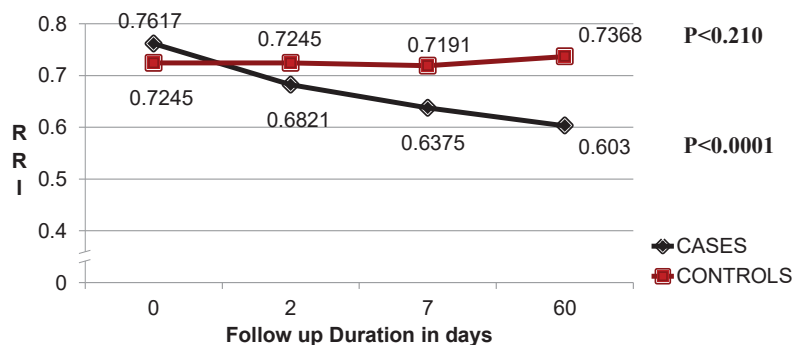


Fig. 3: Follow up RRI of cases and controls

Table 1: Comparison of Parameters between cases and controls

Parameter	Cases	2 months after P value	Controls	Follow up after 2 months	Remarks
eGFR	64.588±32.97	70.12±9.7	0.0021	63.215±18.83	56.134±16.678 Worsened in controls
Mean S. creatinine	1.417±0.546	1.2210±0.3275	0.0045	1.3636±0.442	1.7090±0.599 Worsened in controls
Mean albumin	2.50±0.34	2.61±0.22	0.2131	2.74±0.31	2.53±0.32 Worsened in controls
Mean sodium	130±4.86	135.95±2.52	0.0001	132.32±6.51	129.36±2.79 Lower value in controls
Mean weight	61.89±4.06	58.57±3.58	0.0069	60.82±6.51	62.82±6.51 Weight gain in controls
Mean portal vein diameter	14.07±1.37	11.78±0.99	0.0001	14.23±1.42	12.67±1.04 Reduced less in controls

Table 2: Other studies with Noradrenaline and Terlepressin

Name of the author	Year	No	Intervention done	Results found	Follow up
Alessandriac et al ¹¹	2007	22	Noradrenaline / terlipressin albumin infusion	70% reversal of HRS in noradrenaline group 83% reversal in terlipressin group	30 days
Sharma et al ¹²	2008	40	Noradrenaline and albumin infusion	55% in Noradrenaline and 55% in terlipressin group	30 days
Singh et al ¹³	2012	46	Noradrenaline / terlipressin albumin infusion	43.1% Noradrenaline and 39.1% terlipressin and mortality were similar.	30 days
Goyal et al ¹⁴	2015	41	Noradrenaline / terlipressin albumin infusion	47.6% reversal of HRS in noradrenaline group 45% in terlipressin group	30 days
Present study	2014-2016	48	LVP with Noradrenaline and albumin	100% reversal of HRS in cases. 100% recurrence of HRS in controls.	60 days.

respectively, showed improvement with the p value of 0.00001. In the control group the mean RRI was 0.7245±0.0174 and the follow up mean RRI on the 2nd day, 7th day and after 2 months were 0.7245±0.174, 0.7191±0.0148 and 0.7368±0.01944 respectively, showed worsening, with the p value of 0.2100 (Figure 3).

Comparison of other parameters like e GFR, Serum creatinine, Serum sodium, serum albumin, portal vein diameter and weight of the patients, are shown in Table 1. The eGFR, creatinine, sodium weight and portal vein in the cases showed significant improvement, while in the controls all the parameters showed significant worsening. LVP with nor-adrenaline and albumin, not only improved the RRI, a surrogate

indicator of Renal function, but also improved the eGFR, Serum creatinine and portal vein diameter.

Studies (Table 2) which compared noradrenaline with terlipressin have found noradrenaline to be equally efficacious. We used nor-adrenaline as a vasopressor to avoid PICD and also for its cost benefit compared to terlipressin. The RRI was used to determine the presence of HRS and for follow-up. Our study showed that LVP with noradrenaline and albumin infusion resulted in reversal of HRS in 100% of the cases. In the controls where LVP was not done there was 100% recurrence of HRS. 3 patients died in the controls because of worsening HRS. No deaths were noticed in the cases till the follow-up duration of 2 months.

Discussion

HRS is a disease associated with rapid clinical deterioration and high mortality. Therefore early detection and treatment improves survival rates in individuals with HRS. Liver transplant, which most cannot afford, is the only treatment which could revert HRS. Of the alternative treatment options, LVP with vasopressors and albumin may give some temporary relief.

As shown in Table 2 LVP with noradrenaline and terlipressin was carried out in most studies. In a developing country like India the cost of treatment with terlipressin is prohibitive and may not be affordable to all. The prevalence of cirrhosis in the rural Indian population is 0.2- 0.5 %^[3]. Most of these patients will progress to developing refractory ascites. This large rural population belong to the low socio-economic strata, unable to afford or access Terlipressin. Nor-adrenaline has been shown to be equally efficacious and is a cheaper, cost effective alternative.

No study to date has used the RRI for diagnosis, nor for follow up. While large studies have measured RRI as part of the investigation for cirrhosis with ascites, no standards have been laid down for what we should take as abnormal. The figure of >0.70 RRI has been used by us as per Goyal’s study^[10] but we still don’t know what the RRI is in the normal population. However, using the RRI we have been able to show a significant difference in the values over a 2 month follow –up period. These differences are held also for the eGFR, Serum Creatinine and for the portal vein diameter. All three of these values indicating improvement in the kidney and liver function.

Larger studies need to be done using the RRI both for diagnosis and for follow-up. Using Nor-adrenalin in the protocol of LVP would benefit far more patients at a far lesser cost.

Conclusion

RRI is an affordable, non invasive and easily available tool which should be included as part of a routine Ultrasonographic evaluation in liver cirrhotics, for early detection of HRS and for follow up.

LVP along with Noradrenaline with Albumin infusion (5 gms/ litre of ascitic fluid removed) is as effective as other costlier options.

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