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A Haemodynamic Analysis to Assess the Safe Dose of Carvedilol across Different Child Class of Liver Disease

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Authors' contributions

This work was carried out in collaboration between all authors. Author ZAW designed the study, wrote the protocol, and wrote the first draft of the manuscript. Author RAB managed the literature search, edited the draft and analyzed accuracy. Authors ASB and RM performed the statistical and spectroscopy analysis. Authors SAZ, AHS, IH and SB managed the experimental and review process. All authors read and approved the final manuscript.

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ABSTRACT

Background: Literature regarding safe dose of carvedilol is limited and also safe dose across different child classes of chronic liver disease is not very clear.
Aim: We aimed primarily to study, the effect of reasonably safe dose (12.5 mg) of carvedilol in acute reduction of portal pressure and compared it with chronic reduction of portal pressure, after

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proper optimization of dose of carvedilol. Second aim of our study was to define predictors of response for acute and chronic reduction of portal pressure and to assess difference in dose tolerated and response across different child class on chronic basis.

Methods: One hundred two consecutive patients of cirrhosis of liver with significant portal hypertension were included and hepatic venous pressure gradient was measured at the base line and after 90 minutes of administration of 12.5 mg carvedilol. After proper dose optimization of carvedilol, hepatic venous pressure gradient was again measured after 3 months to assess the chronic response.

Results: The mean age of study population was 58.3±6.6 years. A total of 42.2%, 31.9% and 26.6% patients had child class A, child class B and Child class C cirrhosis, respectively.

Mean pre-drug hepatic venous pressure gradient was 16.75±2.12 mmHg which dropped to 13.07±2.32 mmHg after 90 minutes of administration of 12.5 mg of carvedilol. The mean drop of hepatic venous pressure gradient was 4.5±2.2 mmHg and 2.4±1.9 mmHg among responders and non-responders, respectively. Overall, 51% showed acute response while 49% were non-responders. Low cardiac output and high mean arterial pressure were significantly predicting the acute response, while, low baseline cardiac output was found as an independent predictor.

After dose optimization, number of responders increased from 52 to 62. Mean dose of carvedilol was higher in non–responders as compared to responders, though statistically insignificant ($p>0.05$). Mean reduction of hepatic venous pressure gradient from baseline and after 3 months was 5.5±1.7 mmHg and 2.8±1.6 mmHg among responders and non responders on chronic basis, respectively ($p<0.001$).

Absence of any adverse events (OR 11.3, 95% CI; 1.9-67.8), and more than 2.5 mmHg fall in hepatic venous pressure gradient during acute response (OR 8.7, 95% CI; 3.1-25.3) were found as independent predictors of chronic response ($p<0.05$). Univariate analysis found that no adverse events, no ascites, low baseline cardiac output, more than 2.5 mmHg fall in hepatic venous pressure gradient during acute response, as predictors of chronic response. However, etiology, child class, variceal size (large vs small) and gender were not significantly associated with chronic response

Conclusion: At safe dose and with proper optimization of dose, carvedilol may achieve greater response with minimum side effects among different child classes of liver disease.

Keywords: Carvedilol; hepatic venous pressure gradient; portal hypertension.

1. INTRODUCTION

Portal Hypertension (PTH) and its complication are leading cause of morbidity and mortality in cirrhosis, and these complications lead to either liver transplantation or death [1,2]. Serious complications are esophageal & gastric variceal bleeding, ascites, spontaneous bacterial peritonitis (SBP), hepato-renal syndrome (HRS), portal hypertensive gastropathy, cytopenia, and porto systemic encephalopathy [3]. Recent studies have shown that for these complications to develop, Hepatic venous pressure gradient (HVPG) should increase above 10mmHg and should be above 12 mmHg for variceal bleeding [4,5]. Overall prevalence of varices in an asymptomatic compensated patient is 40% [4] while incidence of variceal development is 6% per year and it doubles if HVPG rises above 10 mmHg and thus cirrhotics with HVPG of > 10 mmHg represent higher risk group. HVPG > 10 mmHg also correlates with higher risk of decompensation & hepatocellular carcinoma (HCC) [6,7]. A good number of meta-analysis has shown that prognosis of cirrhotics patients improve with significant decrease in portal pressure i.e. when target decrease in HVPG (>20% from baseline or to <12 mmHg) is achieved [8,9]. In practice all patients with varices should be treated except for child A patients with small varices without red color signs. Current therapy with propranolol result in a reduction in 1st variceal bleed & mortality compared with placebo [10,11]. Analysis of two recent meta-analysis with sixteen trials do not show difference in bleeding, one meta-analysis has shown variceal band ligation (VBL) as more effective intervention than drug therapy (beta – blocker) in primary prevention of variceal bleeding, although there was no difference in survival [12]. The other meta analysis also showed similar results. Here, the trials with follow up <20 months & unclear bias control were excluded, and it clearly makes no difference in bleeding between VBL & Beta blocker group [13].

Non selective beta blockers (NSBBS) have been the mainstream in pharmacological treatment of portal HTN, preventing first and recurrent variceal bleed and PTH gastropathy & SBP [14]. These drugs achieve HVPG response in 30-40% of patients but reduction in risk of bleeding is to the tune of 45-50% which has been ascribed to decline of azygous blood flow & variceal pressure as well as decreasing the intestinal transit time [14,15]. HVPG can be further reduced when drugs like isosorbide -5 mono nitrate (ISMN), prazosin or statins are added to NSBBS [16,17]. Vasodilating action of carvedilol may cause arterial hypotension and sodium retention and this risk is more relevant to decompensated liver disease [18-20].

The haemodynamic response to carvedilol has been assessed in many earlier studies. A pilot trial on 16 patient's demonstrated fall in HVPG from 16.7 to 13.6 mmHg without significant reduction in azygous blood flow. In this trial mean arterial pressure (MAP) dropped from 94.8 to 84 mmHg and heart rate decrease only in ascites patients. No changes in cardiac output (CO), renal blood flow or systemic vascular resistance were observed [21].

A randomized trial comparing the acute administration of carvedilol to propranolol has shown more effective reduction in portal pressure with carvedilol than propranolol. In this study carvedilol was shown to cause greater reduction in MAP [18]. From this study it was concluded that arterial hypotension may eventually prevent its long term use in cirrhotic patients with hyperdynamic circulation and impaired renal function.

Banres R in 2002 compared carvedilol to propranolol in portal hypertensive patients and showed that proportion of patients achieving haemodynamic response was greater with carvedilol, but on follow up carvedilol caused a significant decrease in MAP, increase in plasma volume. In this study, it was shown that glomerular filtration rate (GFR) remained unchanged with carvedilol and dose of diuretics were more frequently increased in carvedilol group [22]. The long term randomized study using carvedilol for primary prophylaxis of variceal bleeding compared with elective band ligation (EBL) showed significantly lower bleeding rates in carvedilol limb compared to EBL. In this study, haemodynamic response was not evaluated by HVPG measurements and a fixed dose of carvedilol (12.5 mmg) was used [23].

Recently a study evaluated haemodynamic response to carvedilol in propranolol non responders and concluded that carvedilol leads to a significantly greater decrease in HVPG than propranolol. Using carvedilol for primary prophylaxis, a substantial portion of propranolol non-responders achieved a haemodynamic response with improved outcome with regard to prevention of variceal bleeding, hepatic decompensation and death [24].

Therefore primary aim of our study was to assess the effect of reasonably safe dose (12.5 mg) of carvedilol in acute reduction of portal pressure & compare it with chronic reduction of portal pressure after proper optimization of dose of carvedilol. Secondary aims of our study was to assess predictors of response for acute and chronic reduction for portal pressure and to assess difference in response and dose tolerated across different child class of liver disease on chronic basis.

2. PATIENTS AND METHODS

A prospective cohort study was conducted at tertiary care centre of north India from 2010-2013. The study was approved by local Ethics committee of the institute at tertiary centre. Cirrhotic patients referred for haemodynamic evaluation were included in the study. Diagnostic criteria for cirrhosis were based on clinical, biochemical, radiological and if needed on liver biopsy.

The criteria for varices were based on quantitative grading used by Bavino consensus i,e esophageal varices less than 5 mm are small varices and esophageal varices equal to or greater than to 5 mm are considered large varices.

Ascites criteria were used according to international ascites club 2003 i,e grade I-mild [USG based], Grade II-moderate i,e [symmetrical abdominal distension] and Grade III- gross with marked abdominal distension. Inclusion criteria were presence of esophageal varices on upper GI endoscopy, without a previous history of hemorrhage and a baseline HVPG of greater than 12 mmHg. Exclusion criteria's were – Age below 18 years; Severe liver failure defined as INR > 2.5 or bilirubin > 5 mg/dl; Active alcohol consumption (patient with cirrhosis with alcohol abuse have to be abstinent for 3 months); IV drug abuse; Renal failure i,e creatinine > 1.5 mg/dl; HCC; Contraindication to NSBB; Pre or post hepatic cause of PHT; Other malignancy;

Refusal to participate in study. Well informed and written consent was obtained from all the participants in the study.

2.1 Dosing of NSBB

Patients who were eligible for study were first assessed for acute response to carvedilol i.e after baseline HVPG measurement. Patients were given 12.5 mg of carvedilol per oral & HVPG was again measured after 90 minutes to see the acute response to carvedilol. Ninety minutes were used for acute measurement because, the pharmacological aspects of carvedilol and its peak action is between 1-2 hours and most of the studies conducted on carvedilol for acute reduction of portal hypertension are reassessed at 60 to 90 minutes. So we have also chosen 90 minutes for post drug hemodynamic reassessment [18,25].

From next day all patients were started with carvedilol 6.25 mg/day and dose was titrated by steps of 6.25 mg per week. Doses were increased weekly until arterial systolic BP was not less than < 90 mmHg and HR not less than < 55bpm. Compliance with therapy was monitored by recording heart rate (HR) and blood pressure (BP) during clinical visit.

3. DEFINITIONS

3.1 Acute Response

After seeing baseline HVPG and administration of 12.5 mg of carvedilol, Patients HPVG should drop greater than 20% from baseline and or less than 12 mmHg.

3.2 Chronic Response

After optimization of dose of carvedilol and reassessment of HVPG after 3 months, HVPG should drop greater than 20% from baseline and or less than 12 mmHg.

3.3 Chronic Response on no Acute Response

Those patients who had no response to acute administration of carvedilol but showed significant response once carvedilol was given on chronic basis after dose optimization.

Study Design is described in Fig. 1.

Dose optimization was done in all patients who were started with carvedilol. Once doses were optimized, weekly follow up of each patient was done and HVPG was again measured after 3 months. Patients were assessed for side effects. Their BP and HR were measured on each follow up visit.

3.4 Haemodynamic Measurements

Hepatic vein catherization was performed according to standards outlined by Bosch et al [26], under flouroscopic control. 7F balloon tipped catheter was advanced to main Right hepatic vein to measure wedged hepatic venous pressure (WHP). The difference between WHP & free hepatic pressure (FHP) was taken as HVPG. Swangaz catheter was advanced to pulmonary artery for measurement of cardio pulmonary pressures like pulmonary pressure (PA), wedged pulmonary pressures (WPP), right atrial Pressure (RAP) etc. All measurements were repeated thrice and tracings were taken. Mean arterial pressure was measured non-invasively by automatic sphygmomanometer. HR was derived by continuous ECG monitoring and systemic vascular resistance (SVR) as (MAP – RAP/CO x 80).

3.5 Statistical Analysis

Statistical analysis was done by using statistical package for social sciences (SPSS) version 22.0. Descriptive statistics was presented as proportion, Mean ± standard deviation and median with inter-quartile range. Comparative analysis was done by utilizing student's t-test and Chi square test. The univariate and multivariate logistic regression was also used for finding the predictors. A p-value less than 0.05 was considered significant.

4. RESULTS

During the study period, 200 patients of cirrhosis with different etiology were referred for evaluation of PHT with no history of variceal hemorrhage. Among these patients, 35 patients had no esophageal varices, and 25 patients had HVPG < 12 mmHg and were excluded from the study.

Other 38 patients were excluded from study in view of, HCC (10), portal vein thrombosis (PVT), (8), renal failure (10) and refusal to participate (10) in the study. Finally 102 patients with cirrhosis of liver and esophageal varices and with base line HVPG greater than 12 mmHg were included in the study.

Out of 102 patients, 63 (61.85%) were males, and 39 (38.2%) were female patients with the mean age of 58.35±6.62 years. The mean age of female and male patients was 59.3±6.3 and 57.8±6.8 years, respectively.

Main etiologies of cirrhosis were alcoholic Liver disease (ALD), (30.4%), non-alcoholic steatohepatitis (NASH), (25.5%), HCV (19.6%), and HBV (16.7%). Out of these, 43 patients (42.2%) were child A, 32 patients (31.4%) were child B, and 27 patients (26.5%) were child C cirrhosis.

A total of 68 patients (66.7%) had large varices & 34 patients (33.3%) had small varices on upper gastrointestinal endoscopy and 63(61.8)% patients had no ascites while others had mild to moderate ascites. The baseline parameters are shown in Table 1.

Table 1. Baseline characteristics of 102 patients

Parameters	Description
Age (Mean±SD)	58.35±6.62
Gender (Male:Female)	63:39
Child Class (A:B:C)	43:32:27
Etiology (Alcohol :Viral: NASH or Cryptogenic :AIH)	31:37:29: 5
Esophageal Varices (Small : Large)	34:68
Ascites Grade I: Grade II: Grade III	63:6:25:8
Total Bilirubin (mg/dl)	1.96±0.81
Serum Albumin (mg/dl)	3.20±0.49
Prothrombin Time	14.13±1.91
International normalized ratio	1.29±0.16

4.1 Effects of Carvedilol on Acute Reduction of Portal Pressure

A fixed dose of 12.5 mg was given to 102 consecutive patients who fulfilled the inclusion criteria. The acute reduction in portal pressure was assessed after 90 minutes of therapy. Mean pre drug HVPG was 16.75±2.12 mmHg, which dropped to 13.07±2.32 mmHg, after 90 minutes of administration of 12.5 mg of carvedilol.

The mean drop of HVPG was 4.5±2.2 mmHg and 2.4±1.9 mmHg among responders and non responders, respectively. Overall 52 patients (51%) showed acute response i.e < 12 mmhg or 20% drop in HVPG from baseline while 50 patients i.e (49%) were non responders. Mean (± standard deviation) haemodynamic parameters for pre-drug & post-drug are shown in Table 2 for acute response.

In univariate analysis, we found that the baseline low CO and high MAP were significantly predicting the acute response. Gender, child class, etiology, variceal size, presence or absence of ascites and other biochemical parameters were not found to be statistically significant between responders & non responders (Table 3). On multivariate analysis low baseline CO (OR 1.39, 95% CI; 1.11-1.76) and high MAP (OR 0.04, 95% CI; 0.01-0.67) were found as an independent predictors for acute response ($p<0.05$).

4.2 Effect of Carvedilol on Chronic Reduction of PHT

After optimization of dose and reassessment of HVPG after 3 months, total number of responders was increased from 52 (as acute responders) to 62 as chronic responders. However two patients discontinued treatment because of side effects. Mean duration of dose optimization was 15±3 days .Mean reduction of HVPG from baseline and after 3 months was 5.5±1.7 mmHg and 2.8±1.6 mmHg among responders and non responders on chronic basis respectively ($p<0.001$).

Mean dose of carvedilol was higher among non responders (19.2±5.7 mg) as compared to responders (18.7±5.1 mg). However it was not found to be statistically significant. Mean difference between baseline HVPG & HVPG after 3 months was 4.15±2.15 mmHg. Comparison of different haemodynamic parameters between pre-drug (baseline) and post drug chronic (at 3 months) is shown in Table 4.

Major adverse events, which resulted in drug discontinuation was hypotension (in 2 patients), and these patients could not be assessed further and were excluded. Minor adverse events like fatigue, mild dyspnea, headache, temporary impotency, dizziness, etc were resolved without drug discontinuation. These were seen in 9 patients including 7 (non responders) and 2 (responders). Univariate analysis found no adverse events, no ascites, low baseline CO, more than 2.5 mmHg fall in HVPG during acute response, as predictors of chronic response. However, etiology, child class, variceal size (large vs small) & gender were not significantly associated with chronic response (Table 5).

On Multivariate analysis, absence of any adverse events (OR 11.3, 95% CI; 1.9-67.8), and more than 2.5 mmHg fall in HVPG during acute response (OR 8.7, 95% CI; 3.1-25.3) were found as independent predictors of chronic response ($p<0.05$).

4.3 Predictors of Chronic Response with no Prior Acute Response

Comparison of chronic responders who initially had no acute response (10 patients) with those who have neither an acute response nor have a chronic response (50) was also done. High optimized dose of carvedilol (≥18.5 mg) and lesser decrease in HR were found to be significantly associated with chronic response on no acute response ($p<0.05$). Further patients with child A cirrhosis has shown better chronic response as compared to child B and C, but this was not statistically significant (Table 6). Chronic response on no acute response was seen in 66.7% among child A class patients as compared to 36.8% among child B and C class patients.

Table 2. Pre and post therapy (after 90 minutes) comparison of haemodynamic parameters

Haemodynamic Parameter (n=102)	Pre Drug (Baseline) Mean ± SD	Post Drug (after 90 mins) Mean ± SD	P value
MAP(units)mm/hg	89.53±2.42	78.02±1.86	<0.001
HR beats / min	79.45±2.50	61.46±2.13	<0.001
CO litre / min	7.525±0.19	6.502±0.23	<0.001
FHP mmHg	8.28±1.85	9.45±1.91	<0.001
WHP mmHg	25.08±2.55	22.78±2.58	<0.001
HVPG mmHg	16.75±2.12	13.07±2.32	<0.001

MAP-Mean arterial pressure; HR-Heart Rate; CO-Cardiac output; FHP- Free hepatic pressure; WHP- Wedged hepatic pressure; HVPG- Hepatic venous pressure gradient

Table 3. Predictors of acute response (Responders (n=52) vs non-responders (n=50)

Parameters	Response to carvedilol	Mean ± SD / Frequency	P value
Age (years)	Responders	58.25±7.15	0.87
	Non responders	58.46±6.07	
Gender (Male: Female)	Responders	32:20	0.96
	Non responders	31:19	
Child Class (A:B:C)	Responders	21:16:15	0.85
	Non responders	22:16:12	
Etiology (Alcohol: Viral: NASH or cryptogenic: AIH)	Responders	12:20:16:4	0.27
	Non responders	19:17:13:1	
Oesophageal varices (Small: Large)	Responders	16:36	0.57
	Non responders	18:32	
Ascites Grade I: Grade II: Grade III	Responders	32:2:15:3	0.54
	Non responders	31:4:10:5	
Bilirubin (mg/dl)	Responders	1.99±0.85	0.71
	Non responders	1.93±0.78	
Albumin (mg/dl)	Responders	3.16±0.47	0.30
	Non responders	3.26±0.50	
Prothrombin time (sec)	Responders	14.40±1.64	0.14
	Non responders	13.84±2.13	
International normalized ratio	Responders	1.28±0.17	0.54
	Non responders	1.30±0.15	
Cardiac output (L/min)	Responders	7.47±0.19	0.01
	Non responders	7.57±0.18	
Heart rate (beats/min)	Responders	79.71±2.31	0.28
	Non responders	79.18±2.67	
Mean arterial pressure (mmHg)	Responders	90.02±1.27	0.04
	Non responders	89.02±3.14	
FHP (mmHg)	Responders	8.13±1.98	0.40
	Non responders	8.44±1.71	
WHP (mmHg)	Responders	25.35±2.67	0.28
	Non responders	24.80±2.41	
HVPG (mmHg)	Responders	16.98±2.20	0.27
	Non responders	16.52±2.03	

SD-Standard Deviation; NASH-Non Alcoholic Steato-Hepatitis; AIH- autoimmune hepatitis

Table 4. Pre and post therapy (after 3 months) comparison of haemodynamic parameters

Haemodynamic parameter (n=102)	Pre drug Mean ± SD	Post drug Mean ± SD	P value
MAP(units)	89.53±2.42	75.54±1.97	<0.001
HR beats/min	79.45±2.50	57.45±2.44	<0.001
CO liter/min	7.525±0.19	6.38±0.15	<0.001
FHP mmHg	8.28±1.85	9.45±1.90	<0.001
WHP mmHg	25.08±2.55	22.04±2.56	<0.001
HVPG mmHg	16.75±2.12	12.60±2.24	<0.001

Table 5. Predictors of chronic response (Responders (n=62) Vs Non responders (n=38))

Parameters	Response to carvedilol	Mean±SD / Frequency	P value
Age (years)	Responders	58.02±6.92	0.75
	Non responders	58.45±5.98	
Gender (Male: Female)	Responders	40:22	0.35
	Non responders	21:17	
Child class (A:B:C)	Responders	29:19:14	0.60
	Non responders	14:13:11	
Etiology (Alcohol :Viral: NASH or cryptogenic: AIH)	Responders	19: 21:17:5	0.34
	Non responders	12:15:11: 0	
Oesophageal varices (Small : Large)	Responders	22:40	0.34
	Non responders	12:26	
Ascites Grade I: Grade II: Grade III	Responders	42: 1: 16: 3	0.08
	Non responders	21: 4: 8: 5	
Bilirubin (mg/dl)	Responders	1.87±0.82	0.31
	Non responders	2.04±0.77	
Albumin (mg/dl)	Responders	3.23±0.47	0.77
	Non responders	3.20±0.51	
Prothrombin time (secs)	Responders	14.10±1.77	0.98
	Non responders	14.11±2.16	
International normalized ratio	Responders	1.27±0.16	0.15
	Non responders	1.31±0.15	
Cardiac output (L/min)	Responders	7.48±0.18	0.02
	Non responders	7.57±0.18	
Heart rate (beats/min)	Responders	79.61±2.49	0.38
	Non responders	79.16±2.57	
Mean arterial pressure (mmHg)	Responders	89.90±1.25	0.10
	Non responders	89.89±3.57	
Free hepatic venous pressure (mmHg)	Responders	8.11±1.90	0.21
	Non responders	8.58±1.75	
Wedged hepatic venous pressure (mmHg)	Responders	25.05±2.74	0.87
	Non responders	25.13±2.25	
Hepatic venous pressure gradient (mmHg)	Responders	16.74±2.17	0.96
	Non responders	16.76±2.12	
Optimized dose of carvedilol (mg/dL)	Responders	18.7±5.1	0.36
	Non responders	91.7±5.4	
More than 2.5 mmHg decrease in HVPG	Responders	44/62	<0.001
	Non responders	12/38	
Adverse	Responders	2/60	<0.001
	Non responders	9/38	

5. DISCUSSION

Numerous measures have been adopted for treatment of portal hypertension, prevention of variceal bleeding, and rebleeding. The target in pharmacological treatment of portal hypertension should be to reduce the HVPG by at least 20% of baseline value or preferably below 12 mmHg.

This has prompted clinicians and researchers to look for more powerful portal hypotensive agents than propranolol and nodolol either administered alone or in combination with nitrovasodilators. The advantages of medical therapy include safety and systemic effects on correction of detrimental effects induced by portal hypertension.

Table 6. Predictors of chronic response on No acute response (Responders (n=10) Vs Non responders (n=38))

Parameters	Response to carvedilol	Mean±SD/ Frequency	P value
Age (years)	Responders	59.20±6.73	0.32
	Non responders	58.45±5.98	
Gender (Male: Female)	Responders	8:2	0.27*
	Non responders	21:17	
Child Class (A:B:C)	Responders	7:2:1	0.16*
	Non responders	14:13:11	
Etiology (Alcohol :Viral: NASH or Cryptogenic :AIH)	Responders	5:2:2:1	0.26*
	Non responders	12:15:11:0	
Oesophageal Varices (Small : Large)	Responders	5:5	0.28
	Non responders	12:26	
Ascites	Responders	2/10	0.27*
	Non responders	17/38	
Bilirubin (mg/dl)	Responders	1.55±0.76	0.08
	Non responders	2.04±0.77	
Albumin (mg/dl)	Responders	3.51±0.49	0.10
	Non responders	3.20±0.51	
Prothrombin time (sec)	Responders	12.90±1.91	0.10
	Non responders	14.11±2.16	
International normalized ratio	Responders	1.25±0.13	0.21
	Non responders	1.31±0.15	
Cardiac output (L/min)	Responders	7.60±0.13	0.61
	Non responders	7.57±0.18	
Heart rate (beats/min)	Responders	78.90±3.28	0.79
	Non responders	79.16±2.57	
Mean arterial pressure (mmHg)	Responders	89.30±0.95	0.72
	Non responders	88.89±3.58	
Free hepatic venous pressure (mmHg)	Responders	8.20±1.68	0.54
	Non responders	8.58±1.75	
Wedged hepatic venous pressure (mmHg)	Responders	24.20±2.65	0.27
	Non responders	25.13±2.25	
Hepatic venous pressure gradient (mmHg)	Responders	16.00±1.41	0.29
	Non responders	16.76±2.12	
Delta change in cardiac output	Responders	-1.03±0.08	0.69
	Non responders	-1.04±0.11	
Delta change in heart rate	Responders	-15.30±5.07	0.02
	Non responders	-18.42±3.10	
Delta change in mean arterial pressure	Responders	-11.60±1.50	0.90
	Non responders	-11.47±3.43	
Delta change in HVPG	Responders	-2.00±0.47	0.73
	Non responders	-2.18±1.70	
Optimized dose of carvedilol (> 18.5 mg/dL)	Responders	8/10	0.27
	Non responders	21/38	
Adverse	Responders	0/10	0.31*
	Non responders	7/38	

**Fisher's exact test*

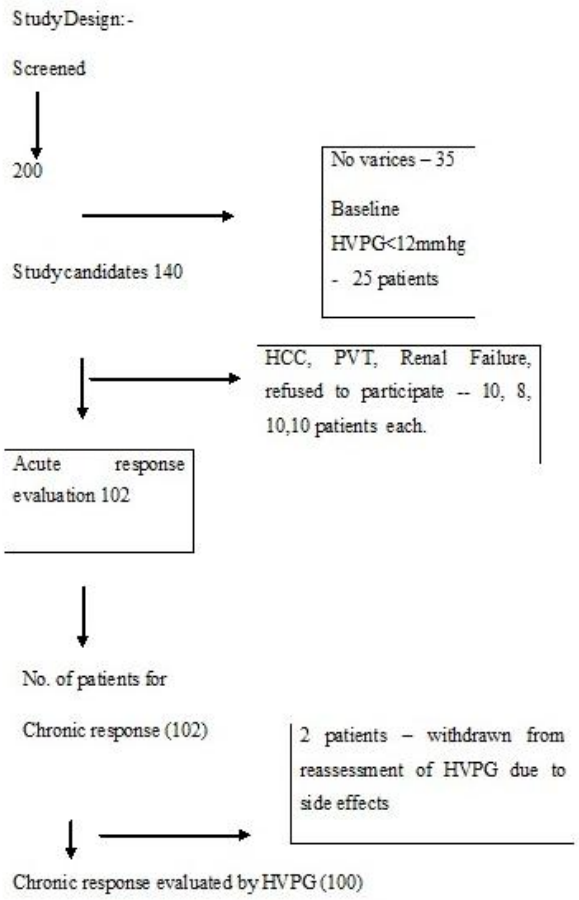

Fig. 1. Summary of study design for the study

Carvedilol a potent 3rd generation, non-selective beta blocker with mild vasodilating properties is considered to be like a combination of beta-blocker and prazosin leading to dose related and marked decrease in portal pressure [27]. There are 8 studies which investigated the acute effects of carvedilol [28-30,18,31-34]. There are 6 studies which investigated chronic effects of carvedilol [35,22,30,31,34]. To date there is one published clinical trial using carvedilol for prevention of variceal hemorrhage [23] and to our knowledge one randomized controlled trial on carvedilol for prevention of variceal rebleeding [36]. There are 3 studies comparing carvedilol with propranolol [22,29,18]. There is one study comparing carvedilol with propranolol plus isosorbide-mono-nitrate [26]. The most of the studies are given below in Table a and b.

Among the acute studies, etiology of cirrhosis were alcohol in 5 studies [30,18,31,33,34], viral in two studies [28,29], both alcohol and viral in another study [32]. The first study to assess the hemodynamic effects of carvedilol was by Forrest et al. [33]. Sixteen patients were administered 25 mg of carvedilol, a greater than 10% of reduction of HVPG was noted in 81% of patients with reduction in HR, CO, MAP. Other studies using similar dose of carvedilol resulted in reduction of HVPG between 21-32% in 41-88% of patients [29,18,31,34]. Lower dose of carvedilol i.e 10-12.5 mg was administered in three studies [30,18,32]. Number of significant responders was 40% and 50% seen in these studies. In our study of hemodynamic evaluation of 102 consecutive patients of cirrhosis of liver with significant portal hypertension on a group of patients with different etiologies of liver disease with different child class of CLD, we found mean pre drug HVPG was (16.75+/-2.12 mmHg) which dropped to (13.07+/-2.32 mmHg) after 90 minutes of administration of 12.5 mg of oral carvedilol. Overall 51% were responders while as 49% were non responders with mean drop of HVPG of 4.5+/-2.2 mmHg and 2.4+/-1.9 mmHg among responders and non responders

respectively. This is in accordance with earlier studies on acute response [29,18,31,34]. Univariate analysis found that baseline low CO and higher MAP were significantly predicting acute response and on multivariate analysis low baseline CO was found as an independent predictor. We do not have clear cut explanation for such results but theoretically speaking dose tolerance by patients with high MAP and low CO is excellent.

There are six studies investigating chronic effects of carvedilol [35,22,30,31,34]. The longest period was 11 weeks in one study; an interesting finding was correlation between acute HVPG reduction and effect after chronic administration in one of the study [29]. In another study by Stanley et al. [31], seven of patients inclusively studied in the acute protocol were unable to complete chronic administration of carvedilol as a result of side effects, in two patients dose was reduced to 12.5 mg per day. This study suggests that at least for study group the administration of 25 mg without attempts to titrate according to response may not be ideal. It is clear that our study is among the few studies which studied both acute and chronic effects of carvedilol on portal hypertension and being the first largest study which used 12.5 mg of carvedilol for acute protocol and dose optimization based strategy for chronic protocol. Keeping in view outcome and side effects seen in Stanley et al. study [31] as discussed above, a titration based strategy was used in our study. Our study tries to look into the difference of response between acute and chronic administration of carvedilol once a safe dose of carvedilol 12.5 mg is used in acute protocol and proper optimization of dose is done to see chronic hemodynamic response. It also studied difference of response between early liver disease and advanced liver disease i.e between child A vs B and C on chronic basis. This study also looks into maximum dose tolerated by different child class of liver disease on chronic basis. Further this study tries to see predictors of chronic and acute response in addition to specific predictors of those chronic responders who are acute non-responders.

Our study shows that number of responders increased from 52 patients (51%) in acute to 62 patients (60%) as chronic responders, two patients discontinued treatment because of side effects. Overall, maximum chronic response of 50% to 72% has been seen in different studies with carvedilol. In Rabergius study [24] with <25 mg of carvedilol used in that study showed a maximum significant response in 72% of patients. Rafael Banares [22] showed that, 58% of patients achieved significant chronic response. It is known that, a correlation between acute and chronic carvedilol can be expected in terms of hemodynamic response [29] but in our study a higher number of patients showed response on chronic basis than acute carvedilol administration probably because of higher mean dose of carvedilol was used in titration protocol on chronic basis i.e 18.7 mg+/-5.1 mg in responders and 19.7 mg+/-5.4 mg in non responder. On multivariate analysis absence of adverse events (OR 11.3, 95% CI 1.9-67.8) and more than 2.5 mmHg fall in HVPG during acute response (OR 8.7, 95% CI; 3.1-25.3) were found as independent predictors of chronic response ($p<0.05$). The possible explanation for such results could be the fact that, patients with less adverse events tolerated a good dose to get good response and patient who had better HVPG drop during acute protocol expected further drop in chronic protocol with increased dose by proper titration.

Major adverse event which resulted in drug discontinuation was hypotension (2 patients) and these patients could not be assessed further as shown in study design;

Minor adverse events like fatigue, mild dyspnea, headache, temporary impotency, dizziness etc were resolved without drug discontinuation. These were seen in 9 patients including 7 non responders and 2 responders as shown below in table. In addition, 2 patients had increase in ascites each belonging to responders and non responder group respectively. In both these patients diuretics were escalated, these both patients belonged to child C class patients.

In a sub group analysis of 50 patients who had no acute significant response, dose of carvedilol 18.5 mg or more and low delta HR were found to be significantly associated with chronic response on no acute response ($p<0.05$). In this group of 50 patients with no acute significant response , 10 patients became chronic responders. Explanations for such results are that higher dose was tolerated by them on chronic basis.

Further in our study patients with child A cirrhosis has shown better chronic response as compared to child B and C but it was not stastically significant, probably a large number of patients is required to get a stastical significance.

Table a. Hemodynamic studies of carvedilol in patients with portal hypertension

Study	Patients	Drug/dose	Child c %	Ascites %	Acute/ chronic study	map	CO	HR	HVPG	Estimated hepatic blood flow	Azygous blood flow	Systemic vascular resistance	Renal blood flow	Sodium excretion
Forrest et al. [19]	16	Carvedilol 25 mg	50	40	Acute-60 min	-15	-13	-7	-19	Ns	ns	Ns	Ns	Na
Sekiyama et al. [18]	10	Carvedilol 10 mg	0	Na	Acute- 60 min	-6	ns	-7	-15	Ns	na	Ns	Na	Na
					90 min	-10	-8	-8	-17	Ns	na	Ns	Na	Na
Stanley et al. [17]	17	Carvedilol 25 mg	24	65	Acute 60 min	-4	-7	-3	-21	Ns	na	Ns	Na	Na
	10	Carvedilol 25 mg		60	Chronic 4 weeks	Ns	ns	-17	-16	Ns	na	Ns	Na	Ns
Banares et al. [16]	14	Carvedilol 25 mg	14	50	Acute 60 and 120min	-17	-10	-11	-21	-10	-20	-10	Na	Na
	14	Propanolol IV	21	50	Acute 60 min	ns	-23	-16	-13	-14	-24	+20	NA	NA
Tripathi et al. [15]	10	Carvedilol 12.5 mg	20	40	Acute 60 min	-10	-12	-10	-24	-58	NA	NS	NA	NA
	9	Carvedilol 12.5 mg	11	33	Chronic 4weeks	NS	NS	-19	-43	-65	NA	NS	NA	NA
De et al. [14]	18	Carvedilol 25 mg	11	67	Acute 90 min	-11	NA	-9	-28	NA	NA	NA	NA	NA
	18	Propanolol 80 mg	6	89	Acute 90 min	NS	NA	-14	-23	NA	NA	NA	NA	NA
	17	Carvedilol 12.5 mg	6	65	Chronic 7 days	-16	NA	-15	-28	NA	NA	NA	NA	NA
	18	Propanolol 80 mg	6	89	Chronic 7 days	-6.2	NA	-25	-22	NA	NA	NA	NA	NA
Banares et al. [13]	26	Carvedilol 31 mg	12	39	Chronic 11 weeks	-11	-15	-16	-19	NS	-14	NS	NA	NS
	25	Propanolol 73mg	16	24	Chronic 11 weeks	-5	-22	-24	-12	-19	-24	+19	NA	NS
Lin et al. [12]	11	Carvedilol 25 mg	NA	NA	Acute 90 min	NS	-18	-11	-19	+29	NA	NS	NA	NA
		Propanolol 40mg+ISMN 20 mg	NA	NA	Acute 90 min	-10	-23	-15	-10	NS	NA	NS	NA	NA
Bruha et al. [11]	36	Carvedilol 25 mg	19	NA	Chronic 30 days	-8	NA	-13	-16	NA	NA	NA	NA	NA
Silkauskaite et al. [20]	10	Carvedilol25 mg	NA	NA	Acute-60min	NA	NA	NA	-32	NA	NA	NA	NA	NA
	9	Carvedilol 25 mg			Chronic 14 days	NA	NA	NA	-26	NA	NA	NA	NA	NA

Table b. Hemodynamic studies of carvedilol versus propranolol in patients with portal hypertension

Study	Patients(n)	Drug/dose	Child c %	Ascites %	Acute/ chronic study	MAP	CO	HR	HVPG	Estimated hepatic blood flow	Azygous blood flow	Systemic vascular resistance	Renal blood flow	Sodium excretion
Banares et al. [16]	14	Carvedilol 25 mg	14	50	Acute 60 and 120min	-17	-10	-11	-21	-10	-20	-10	Na	Na
	14	Propanolol IV	21	50	Acute 60 min	ns	-23	-16	-13	-14	-24	+20	NA	NA
De et al. [14]	18	Carvedilol 25 mg	11	67	Acute 90 min	-11	NA	-9	-28	NA	NA	NA	NA	NA
	18	Propanolol 80 mg	6	89	Acute 90 min	NS	NA	-14	-23	NA	NA	NA	NA	NA
	17	Carvedilol 12.5 mg	6	65	Chronic 7 days	-16	NA	-15	-28	NA	NA	NA	NA	NA
	18	Propanolol 80 mg	6	89	Chronic 7 days	-6-2	NA	-25	-22	NA	NA	NA	NA	NA
Banares et al. [13]	26	Carvedilol 31 mg	12	39	Chronic 11 weeks	-11	-15	-16	-19	NS	-14	NS	NA	NS
	25	Propanolol 73 mg	16	24	Chronic 11 weeks	-5	-22	-24	-12	-19	-24	+19	NA	NS
Lin et al. [12]	11	Carvedilol 25 mg	NA	NA	Acute 90 min	NS	-18	-11	-19	+29	NA	NS	NA	NA
		Propanolol 40mg+ISMN 20 mg	NA	NA	Acute 90 min	-10	-23	-15	-10	NS	NA	NS	NA	NA

6. CONCLUSION

In conclusion our study being the largest study which has used fixed dose of carvedilol in acute protocol and titration based dose of carvedilol in chronic protocol and has shown it as excellent drug for significant reduction of portal hypertension with minimum side effects and excellent tolerability.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

REFERENCES

1. Bosch J, Abraldes JG, Groszmann RJ. Current management of portal hypertension. J Hepatol. 2003;38:S54-S68.
2. Vargas V, Rimola A, Casanovas T, Castells L, Navasa M, Baliellas C, et al. Applicability of liver transplantation in Catalonia at the end of the millennium. A prospective study of adult patient selection for liver transplantation. Transpl Int 2003; 16:270-275.
3. Bosch J, Berzigotti A, Garcia-Pagan JC, Abraldes JG. The management of portal hypertension: Rational basis, available treatments and future options. J Hepatol. 2008;48:S68-S92.
4. Groszmann RJ, Garcia-Tsao G, Bosch J, Grace ND, Burroughs AK, Planas R, et al. Portal Hypertension Collaborative Group. Beta-blockers to prevent gastro esophageal varices in patients with cirrhosis. N Engl J Med. 2005;353:2254-2261.
5. Groszmann RJ, Bosch J, Grace ND, Conn HO, Garcia-Tsao G, Navasa M, et al. Haemodynamic events in a prospective randomized trial of propranolol versus placebo in the prevention of a first variceal hemorrhage. Gastroenterology. 1990; 99:1401-1407.
6. Ripoll C, Groszmann R, Garcia Tsao G, Grace N , Burroughs A, Planas R, et al. Portal hypertension collaborative group. Hepatic venous pressure gradient predicts clinical decompensation in patients with compensated cirrhosis. Gastroenterology 2007;133:481-488.
7. Ripoll C, Groszmann R, Garcia Tsao G, Grace N, Burroughs A, Planas R, et al. Portal hypertension collaborative group; hepatic venous pressure gradient predicts development of hepatocellular carcinoma independently of severity of cirrhosis. J H hepatol. 2009;50:923-928.
8. Abraldes JG, Tarantino I, Turns J, Garcia-Pagan JC, Rodés J, Bosch J. Hemodynamic response to pharmacological treatment of Portal Hypertension and long term prognosis of cirrhosis. Hepatology. 2003;37:902-908.
9. Albillos A, Banares R, Gonzalaz M, Ripoll C, Gonzalez R, Catalina MV, et al. Value of the hepatic venous pressure gradient to monitor drug therapy for portal hypertension: A meta-analysis. Am J Gastroenterol. 2007;102:1116-1126.
10. Cheng JW, Zhu L, Gu MJ, Song ZM. Meta analysis of propranolol effects on gastrointestinal hemorrhage in cirrhotic patients. World J Gastroenterol. 2003; 9:1836-1839.
11. Hayes PC, Davis JM, Lewis JA, Bouchier IA. Meta analysis of value of propranolol in prevention of variceal hemorrhage. Lancet 1990;336:153-156.
12. Tripathi D, Graham C, Hayes PC. Variceal band ligation versus beta-blockers for primary prevention of variceal bleeding: A meta-analysis. Eur J Gastroenterol Hepatol 2007;19:835-845.
13. Gluud LL, Klingenberg S, Nikolova D, Gluud C. Banding ligation versus beta blockers as primary prophylaxis in esophageal varices: Systematic review of randomized trials. Am J Gastroenterol. 2007;102:2842-2848.
14. Garcia-Tsao G, Bosch J, Management of varices and variceal hemorrhage in cirrhosis. N Engl J Med. 2010;362:823-32.
15. Tsochatzis EA, Bosch J, Burroughs AK. New therapeutic paradigm for patients with cirrhosis. Hepatology. 2012;56:1983-92.
16. Bureau C, Peron JM, Alric L, Morales J, Sanchez J, Barange K, et al. “A La Carte” treatment of portal hypertension: Adapting medical therapy to hemodynamic response for the prevention of bleeding. Hepatology. 2002;36:1361-6.
17. Abraldes JG, Albillos A, Banares R, Turnes J, González R, García-Pagán JC. Simvastatin lowers portal pressure in patients with cirrhosis and portal hypertension: a randomized controlled trial. Gastroenterology. 2009;136:1651-8.
18. Banares R, Moitinho E, Piqueras B, Casado M, Garcia-Pagan JC, De Diego A, et al. Carvedilol, a new non selective beta-blocker with intrinsic anti-alpha 1-adrenergic activity, has a greater portal

hypotensive effect than propranolol in patients with cirrhosis. Hepatology. 1999; 30:79-83.
19. Hamdan Al-Ghamdi. Carvedilol in the treatment of portal hypertension. Saudi J Gastroenterol. 2011;17:155-158.
20. Hemstreet BA. Evaluation of carvedilol for the treatment of portal hypertension. Pharmacotherapy. 2004;24:94-104.
21. Bosch J, Garcia-pagan JC. Complications of cirrhotic Portal hypertension. J Hepatol 2000;32:141-56.
22. Banares R, Moitinho E, Matilla A, Garcia-pagan JC, Lampreave JL, Piera C, et al. Randomized comparison of long-term carvedilol and propranolol administration in the treatment of portal hypertension in cirrhotic. Hepatology. 2002;36:1367-73.
23. Tripathi D, Ferguson JW, Kochar N, Leithead JA, Therapondos G, McAvoy NC, et al. Randomized controlled Trial of carvedilol versus variceal band ligation for the prevention of the first variceal bleed. Hepatology. 2009;50:825-833.
24. Reiberger T, Ulbrich G, Ferlitsch A, Payer BA, Schwabl P, Pinter M, et al. Carvedilol for primary prophylaxis of variceal bleeding in cirrhotic patients with hemodynamic non response to propranolol. Gut. 2013; 62:1634-1641.
25. Ruffolo RRJr, Gellai M, Hiehle JP, Willette RN. The pharmacology of carvedilol. Eur J Clin Pharmacol. 1990;38:S82-8.
26. Bosch J, Garcia-pagan JC, Berzigotti A, Abraldes JG. Measurement of portal pressure and its role in the management of chronic liver disease. Semin Liver Dis 2006;26:348-362.
27. Bosch J. Carvedilol for portal hypertension in patients with cirrhosis. Hepatology. 2010;51:2214-8.
28. Lin HC, Yang YY, Hou MC, Huang YT, Lee FY, Lee SD. Acute administration of carvedilol is more effective than propranolol plus isosorbide-5-mononitrate in the reduction of portal pressure in patients with viral cirrhosis. Am J Gastroenterol. 2004;99:1953-1958.
29. De BK, Das D, Sen S, Biswas PK, Mandal SK, Majumdar D, et al. Acute and 7-day portal pressure response to carvedilol and propranolol in cirrhotics. J Gastroenterol Hepatol. 2002;17:183-189.
30. Tripathi D, Therapondos G, Lui HF, Stanley AJ, Hayes PC. Hemodynamic effects of acute and chronic administration of low-dose carvedilol, a vasodilating beta-blocker, in patients with cirrhosis and portal hypertension. Aliment Pharmacol Ther. 2002;16:373-380.
31. Stanley AJ, Therapondos G, Helmy A, Hayes PC. Acute and chronic haemodynamic and renal effects of carvedilol in patients with cirrhosis. J Hepatol. 1999;30:479-484.
32. Sekiyama T, Komeichi H, Nagano T, Ohsuga M, Terada H, Katsuta Y, et al. Effects of the alpha-/beta-blocking agent carvedilol on hepatic and systemic hemodynamics in patients with cirrhosis and portal hypertension. Arzneimittel forschung. 1997;47:353-355.
33. Forrest EH, Bouchier IA, Hayes PC. Acute haemodynamic changes after oral carvedilol, a vasodilating beta-blocker, in patients with cirrhosis. J Hepatol. 1996; 25:909-915.
34. Silkauskaite V, Pranculis A, Kupcinskas J, Petrenkiene V, Kupcinskas L. Acute and 14-days hepatic venous pressure gradient response to carvedilol and nebivolol in patients with liver cirrhosis. A pilot study. J Hepatol. 2009;50:226.
35. Bruha R, Vitek L, Petrtyl J, Lenicek M, Urbanek P, Zelenka J, et al. Effect of carvedilol on portal hypertension depends on the degree of endothelial activation and inflammatory changes. Scand J Gastroenterol. 2006;41:1454-1463.
36. Gin-Ho Lo, Wen-Chi Chen, Huay-Min Wang, Hsien-Chung Yu. Randomised, controlled trial of carvedilol versus nadolol plus isosorbide mononitrate for the prevention of variceal rebleeding. Journal of gastroenterology and Hepatology. 2012; (27):1681-1687.

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