

After Proper Optimization of Carvedilol dose, do Different Child Classes of Liver Disease Differ in Terms of dose Tolerance and Response on a Chronic Basis?

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ABSTRACT

Background/Aims: Literature regarding safe doses of carvedilol is limited, and safe doses across different Child classes of chronic liver disease are not clear. **Patients and Methods:** A total of 102 consecutive cirrhotic patients with significant portal hypertension were included in this study. Hepatic venous pressure gradient was measured at baseline and 3 months after dose optimization. **Results:** A total of 102 patients (63 males, 39 females) with a mean age of 58.3 ± 6.6 years were included. Among these patients, 42.2% had Child Class A, 31.9% had Class B, and 26.6% had Child Class C liver disease. The mean baseline hepatic venous pressure gradient was 16.75 ± 2.12 mmHg, and after dose optimization and reassessment of hepatic venous pressure gradient at 3 months, the mean reduction in the hepatic venous pressure gradient was 5.5 ± 1.7 mmHg and 2.8 ± 1.6 mmHg among responders and nonresponders respectively. The mean dose of carvedilol was higher in nonresponders (19.2 ± 5.7 mg) than responders (18.75 ± 5.1 mg). However, this difference was not statistically significant ($P > 0.05$). The univariate analysis determined that the absence of adverse events, the absence of ascites, and low baseline cardiac output were significantly associated with chronic response, whereas, the etiology, Child class, variceal size (large vs small), and gender were not. On multivariate analysis, the absence of any adverse event was determined to be an independent predictor of chronic response (OR 11.3, 95% CI; 1.9–67.8). **Conclusion:** The proper optimization of the dose of carvedilol, when administered chronically, may enable carvedilol treatment to achieve a greater response with minimum side effects among different Child classes of liver disease.

Key Words: Cirrhosis, hepatocellular carcinoma, varices

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The prevalence of varices in asymptomatic compensated patients is 40%.^[1] The incidence of variceal development is 6% per year, and it doubles if hepatic venous pressure gradient (HVPG) rises above 10 mmHg. Thus, cirrhotics with HVPG of >10 mmHg are at higher risk of variceal development. HVPG >10 mmHg also correlates with a higher risk of decompensation and hepatocellular

carcinoma (HCC).^[2,3] A good number of meta-analyses have shown that the prognosis of cirrhotic patients improve with a significant decrease in portal pressure.^[4,5] In practice, all patients with varices should be treated, except for Child A patients with small varices without the red color sign.

The current therapy with propranolol results in a reduction in first variceal bleed and mortality compared with placebo.^[6,7] Two recent meta-analyses that reviewed a total of 16 trials did not show any difference in bleeding. One meta-analysis showed that variceal band ligation (VBL) was a more effective intervention than drug therapy in the primary prevention of variceal bleeding, without any difference in survival.^[8] The other meta-analysis had similar results. Here, trials with follow up <20 months and unclear bias control

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were excluded, and no difference in bleeding between VBL and beta-blocker treatment was observed.^[9]

The mainstream pharmacological treatment of portal hypertension (PHT), that is, nonselective beta-blockers (NSBB) propranolol and nadolol, prevent first and recurrent variceal bleeding, PHT, gastropathy, and spontaneous bacterial peritonitis.^[10] These drugs achieve a HVPG response in 30%–40% of patients and a reduction in risk of bleeding in 45%–50%, which has been ascribed to the decline of azygous blood flow and variceal pressure and the decrease in intestinal transit time.^[10,11]

When added to NSBBs, drugs, such as isosorbide-5 mononitrate, prazosin, and statins, help decrease hepatic vascular tone and, thus, can convert many nonresponders into responders.^[12,13] Additionally, HVPG can be further reduced with these drugs.

The hemodynamic response to carvedilol has been assessed in many earlier studies. A pilot trial on 16 patients demonstrated a fall in HVPG from 16.7 to 13.6 mmHg without a significant reduction in azygous blood flow with carvedilol treatment. In this trial, the mean arterial pressure (MAP) dropped from 94.8 to 84 mmHg in all patients, and heart rate decreased only in ascites patients. No change in cardiac output (CO), renal blood flow, or systemic vascular resistance was observed.^[14]

A randomized trial comparing the acute administration of carvedilol and propranolol showed that carvedilol more effectively reduced portal pressure than propranolol. In this study, carvedilol was shown to cause a greater reduction in MAP than propranolol.^[15] However, arterial hypotension may eventually prevent the long-term use of carvedilol in cirrhotic patients with hyperdynamic circulation and impaired renal function.

A study evaluating the hemodynamic response to carvedilol in propranolol nonresponders showed that carvedilol leads to a significantly greater decrease in HVPG than propranolol. Using carvedilol for primary prophylaxis, a substantial portion of propranolol nonresponders achieved a hemodynamic response with improved outcome with regard to prevention of variceal bleeding, hepatic decompensation, and death. That study showed that carvedilol is well tolerated and is an effective treatment for PHT. Carvedilol had greater efficacy in propranolol nonresponders, with up to 72% of patients treated with carvedilol showing an HVPG response.

That study also showed that increasing the dose of carvedilol above 12.5 mg can increase unwanted systemic and renal side effects without increasing its portal hypotensive effect; thus,

further studies are needed to determine the optimal dose of carvedilol. Furthermore, the optimal dose of carvedilol may vary across different Child classes, and thus, the response to carvedilol with respect to its optimal dose across different Child classes may also vary.^[16]

The primary aim of the present study was to examine the effect of carvedilol on the chronic reduction of portal pressure after proper dose optimization.

PATIENTS AND METHODS

This was a prospective cohort study conducted at a tertiary care center in north India from 2010 to 2013. The study was approved by the local ethics committee of the institute. Cirrhotic patients referred for hemodynamic evaluation were included in the study. All patients with cirrhosis related to hepatitis B infection were started on treatment before the study.

Changes in liver test results, especially bilirubin, albumin, prothrombin time, and international normalized ratio (INR), before and 3 months after carvedilol treatment were assessed.

The inclusion criteria were the presence of esophageal varices on upper gastrointestinal endoscopy without a previous history of hemorrhage and a baseline HVPG of greater than 12 mmHg.

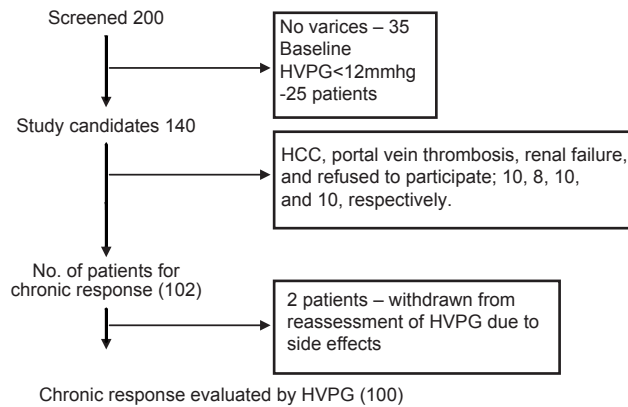
The exclusion criteria were patients younger than 18 years; severe liver failure (INR >2.5 or bilirubin >5 mg/dL); active alcohol consumption (patients with cirrhosis with alcohol abuse have to be abstinent for 3 months); IV drug abuse; renal failure (acute or chronic), that is, creatinine >1.5 mg/dL; HCC; contraindication to NSBB; pre- or posthepatic cause of PHT; and refusal to participate in the study. Well-informed, written consent was obtained from all participants in the study.

Dosing of NSBB

After 8 h of fasting, baseline HVPG was measured. Starting the next day, all patients were given 6.25 mg/day carvedilol, and the dose was titrated by steps of 6.25 mg per week. The dose was increased weekly until arterial systolic blood pressure was <90 mmHg and heart rate (HR) was <55 bpm. Compliance with therapy was monitored by recording HR and BP during clinical visits.

Definitions

Chronic response: After optimization of carvedilol dose and reassessment of HVPG after 3 months of treatment, HVPG should drop by more than 20% from baseline and/or less than 12 mmHg.



Study design

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

Hemodynamic measurements

Hepatic vein catheterization was performed according to the standards outlined by Bosch *et al.*^[17] under fluoroscopic control. A 7F balloon tipped catheter was advanced to the main right hepatic vein to measure wedged hepatic venous pressure (WHP). The difference between WHP and free hepatic pressure (FHP) was the HVPG. A Swangaz catheter was advanced to the pulmonary artery for measurement of cardiopulmonary pressures, such as pulmonary artery pressure (PAP), wedged pulmonary pressure (WPP), and right atrial pressure (RAP). All measurements were repeated three times, and tracings were taken. MAP was measured noninvasively using an automatic sphygmomanometer. HR was derived by continuous ECG monitoring and systemic vascular resistance (SVR), which was calculated as $MAP - RAP / CO \times 80$.

Statistical analysis

The statistical analysis was performed using statistical package for social sciences (SPSS) version 22.0. Descriptive statistics are presented as proportions, means \pm standard deviation, and medians with interquartile range. Comparative analyses were performed using the Student's *t*-test and Chi-square test. Univariate and multivariate logistic regression analyses were also used to determine predictors of chronic response. A *P* value of less than 0.05 was considered significant.

RESULTS

On upper gastrointestinal endoscopy, 68 patients (66.7%) had large varices, and 34 patients (33.3%) had small varices. Sixty-three patients (61.8%) had no ascites, whereas the

other patients had mild-to-moderate ascites. The baseline parameters are shown in Table 1.

Effect of carvedilol on chronic reduction of PHT

After optimization of carvedilol dose and reassessment of HVPG after 3 months of treatment, the total number of chronic responders were 62. However, two patients discontinued treatment because of side effects. The mean duration of dose optimization was 15 ± 3 days. The mean reduction in the HVPG after 3 months was 5.5 ± 1.7 mmHg among responders and 2.8 ± 1.6 mmHg among nonresponders ($P < 0.001$).

The mean dose of carvedilol was higher among nonresponders (19.2 ± 5.7 mg) than responders (18.7 ± 5.1 mg). However, this difference was not statistically significant. The mean difference between baseline HVPG and HVPG after 3 months of treatment was 4.15 ± 2.15 mmHg. Comparisons of the different hemodynamic parameters at baseline and after 3 months are shown in Table 2.

A major adverse event that resulted in drug discontinuation was hypotension; this occurred in two patients who, therefore, could not be assessed further and were excluded from the study. Minor adverse events, such as fatigue, mild dyspnea, headache, temporary impotency, and dizziness, were resolved without drug discontinuation, and these events occurred in nine patients, including seven nonresponders and two responders. In addition, two patients, one responder, and one nonresponder, both of whom had Child Class C disease, showed an increase in ascites. In both of these patients, diuretics were escalated.

The univariate analysis found that the absence of adverse events, the absence of ascites, and low baseline CO were predictors of chronic response. However, etiology, Child class, variceal size (large vs small), and gender were not significantly associated with chronic response [Table 3]. The multivariate analysis found that the absence of adverse event (OR 11.3, 95% CI; 1.9–67.8) was an independent predictor of chronic response [Table 3].

DISCUSSION

This is one of only a few studies that have assessed the chronic reduction of HPVG after the administration of carvedilol optimized to the proper dose (in this case after 3 months of treatment). Furthermore, this study examined the following issues in addition to identifying predictors of chronic reduction of HVPG.

- The difference in the chronic response to carvedilol between patients with early liver disease and advanced liver disease, that is, Child A, B, and C disease

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)	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

NASH: Nonalcoholic steatohepatitis; AIH: Autoimmune hepatitis

Table 2: Comparison of hemodynamic parameters pre- and posttherapy (after 3 months)

Hemodynamic parameter (n=102)	Mean±SD		P
	Predrug	Postdrug	
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 (L/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
SBP (mmHg)	118±2.9	90±2.2	<0.001

MAP: Mean arterial pressure; HR: Heart rate; CO: Cardiac output; FHP: Free hepatic pressure; WHP: Wedged hepatic venous pressure; HVPG: Hepatic venous pressure gradient; SBP: Systolic blood pressure

- The relationship between higher carvedilol doses and chronic response.

Carvedilol causes a much greater decrease in portal pressure than propranolol. Thus, administering another alpha-1 blockade drug in addition to propranolol may increase the number of patients with significant hemodynamic responses. A randomized trial comparing the acute administration of carvedilol to propranolol showed a more effective reduction in portal pressure and a greater decrease in MAP with carvedilol than with propranolol.^[15] A second randomized trial assessing the efficacy and safety of the long-term use of carvedilol compared with propranolol in portal hypertensive patients^[18] showed that the hemodynamic response was greater with carvedilol than propranolol. That study also showed that after a median observation period of 3 months, carvedilol caused a significant decrease in MAP and a significant increase in plasma volume and body weight, with no change in glomerular filtration rate (GFR). Another long-term randomized trial using carvedilol for primary prophylaxis of variceal bleeding compared with EBL demonstrated a lower bleeding rate under carvedilol than EBL limb.^[19]

This study was a hemodynamic evaluation of 102 patients after baseline assessment of HVPG and optimization of the dose of carvedilol based on BP and HR. HVPG was re-assessed after 3 months of carvedilol treatment. We found that chronic administration of carvedilol can generate a significant HVPG response in propranolol nonresponders^[16] without any significant side effects. This supports the results of an earlier study by Tripathi *et al.*^[19] who found that carvedilol is safe for chronic administration. A low dose of carvedilol (<25 mg) is as effective as a relatively high dose (25–50 mg/day) in decreasing HVPG with a lower risk of causing arterial hypotension, and in most cases, dose adjustment is limited to 6.25–125.5 mg/day.^[20]

In our study, the number of patients with chronic responses and the magnitude of those responses were assessed, and predictors of chronic response were determined. Furthermore, the following topics were examined in this study: (1) The relationship between chronic response across different Child classes; (2) dose requirements in responders across different Child classes; and (3) different responses of the different Child classes to their respective optimized doses. As discussed by Bosch,^[20] low-dose carvedilol (<25 mg/day) is as effective as high-dose carvedilol (25–50 mg/day), and this study showed that the optimal dose for each Child class is more important than the simple distinction between low dose and high dose when administering carvedilol on a chronic basis.

In our study, after dose optimization and assessment of HVPG after 3 months of treatment, the response rate was, 60.68%. Two patients discontinued treatment because of side effects. The mean dose was higher in the nonresponders (19.7 ± 5.4 mg) than in the responders (18.7 ± 5.1 mg), although this difference was not statistically significant. The mean difference between baseline HVPG and HVPG after 3 months of treatment was 5.5 ± 1.7 mmHg among responders and 2.8 ± 1.6 mmHg among nonresponders.

Less adverse events, the absence of ascites, low-baseline CO, high-delta FHVP, low-delta WHP, and low-delta HVPG were found to be predictors of chronic response to carvedilol treatment. However, etiology, Child class, variceal size (large vs small) and gender were not significantly associated with chronic response to carvedilol treatment by univariate analysis.

The multivariate analysis showed that the absence of any adverse event (OR 11.3, 95% CI; 1.9–67.8) was an independent predictor of chronic response to carvedilol treatment ($P < 0.05$). Patients with Child A cirrhosis showed a better chronic response than patients with Child B and C cirrhosis, although this difference was not statistically significant.

Table 3: Predictors of chronic response (responders (n=62) versus nonresponders (n=38))

Parameters	Response to carvedilol	Mean±SD/frequency	P
Age (years)	Responders	58.02±6.92	0.75
	Nonresponders	58.45±5.98	
Gender (male:female)	Responders	40:22	0.35
	Nonresponders	21:17	
Child Class (A:B:C)	Responders	29:19:14	0.60
	Nonresponders	14:13:11	
Etiology (alcohol:viral:NASH or cryptogenic:AIH)	Responders	19:21:17:5	0.34
	Nonresponders	12:15:11:0	
Esophageal varices (small:large)	Responders	22:40	0.34
	Nonresponders	12:26	
Ascites (no:mild:minimal:moderate)	Responders	42: 1:16:3	0.08
	Nonresponders	21:4:8:5	
Bilirubin (mg/dL)	Responders	1.87±0.82	0.31
	Nonresponders	2.04±0.77	
Albumin (mg/dL)	Responders	3.23±0.47	0.77
	Nonresponders	3.20±0.51	
Prothrombin time (s)	Responders	14.10±1.77	0.98
	Nonresponders	14.11±2.16	
International normalized ratio	Responders	1.27±0.16	0.15
	Nonresponders	1.31±0.15	
Cardiac output (L/min)	Responders	7.48±0.18	0.02
	Nonresponders	7.57±0.18	
Heart rate (beats/min)	Responders	79.61±2.49	0.38
	Nonresponders	79.16±2.57	
Mean arterial pressure (mmHg)	Responders	89.90±1.25	0.10
	Nonresponders	89.89±3.57	
Free hepatic venous pressure (mmHg)	Responders	8.11±1.90	0.21
	Nonresponders	8.58±1.75	
Wedge hepatic venous pressure (mmHg)	Responders	25.05±2.74	0.87
	Nonresponders	25.13±2.25	
Hepatic venous pressure gradient (mmHg)	Responders	16.74±2.17	0.96
	Nonresponders	16.76±.12	
Optimized dose of carvedilol (mg)	Responders	18.7±5.1	0.36
	Nonresponders	19.2±5.7	
More than 2.5 mmHg decrease in HVPG	Responders	44/62	<0.001
	Nonresponders	12/38	
Adverse	Responders	2/60	<0.001
	Nonresponders	9/38	

HVPG: Hepatic venous pressure gradient; SD: Standard deviation; NASH: Nonalcoholic steatohepatitis; AIH: Autoimmune hepatitis

CONCLUSIONS

We have demonstrated that PHT can be significantly decreased with chronic carvedilol treatment. We observed that 60.6% of patients had a chronic response after dose optimization. Drug withdrawal due to side effects occurred in two patients, and all other patients tolerated the drug very well. Child cirrhosis A disease showed better chronic response than Child B and C disease. Additional studies with larger sample sizes are needed to determine if an increased dose in patients with Child A disease helps convert acute nonresponders to responders without side effects, especially patients who show a greater decrease in HR on carvedilol

treatment. However, based on the results of this study, a dose > 18.5 mg, especially in patients with Child A disease, is a reasonable one for chronic administration. Furthermore, carvedilol should be the beta-blocker of choice for the treatment of chronic liver disease, except in hypotensive patients and patients with refractory ascites.

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