ORIGINAL ARTICLE ASIAN JOURNAL OF MEDICAL SCIENCES

A Hemodynamic Study to assess response, tolerance and dose optimization of Carvedilol in Child Class A patients with Portal Hypertension

Shaheen Nazir[1], Zeeshan Ahmed[2], Muzzafer Mohamad[3], Afaq Ahmad[4], Wasim Ahmed[5], Inaam-ul-Haq[6], Altaf Hussain[7]

[1]Consultant, Department of Health and Family Welfare (J and K). Presently Consultant in Department of Gastroenterology in Superspeciality Hospital Shireen Bagh, Srinagar, India, [2]Ex Associate Professor, Institute of Liver and Biliary Sciences, New Delhi, Presently Senior Consultant, Department of Gastroenterology, Superspeciality Hospital Shireen Bagh, Srinagar, India, [3]Consultant Gastroenterology, Noora Hospital, Srinagar, India, [4]Assistant Professor, Department of Clinical Hematology, Sher-I-Kashmir Institute of Medical Sciences, Soura, Srinagar, India, [5]Senior Clinical Fellow Cardiology, Chelsea and Westminster NHS Trust, London, United Kingdom, [6]Consultant Department of Community Medicine, Government Medical College, Srinagar, India, [7]Professor and Head of Department of Gastroenterology, Sher-I-Kashmir Institute of Medical Sciences, Soura, Srinagar, India

Submission: 18-04-2021 Revision: 24-07-2021 Publication: 01-08-2021

ABSTRACT

Background: Carvedilol has an established role in Chronic Liver disease (CLD) associated Portal Hypertension, however its role in specific subclasses of CLD has not been studied, neither the factors leading to non-response thereby predisposing such patients to variceal bleed with empiric therapy. **Aims and Objectives:** The purpose of this study was. 1. To evaluate the hemodynamic response to Carvedilol and optimum dosage in patients of CTP Class A Cirrhosis. 2. To determine any clinical variables that would help in differentiating responders from non-responders. **Materials and Methods**: In forty-three consecutive patients of chronic liver disease Child Turcotte Pugh (CTP) Class A with esophageal varices, Hepatic Venous Pressure Gradient (HVPG) was measured at baseline, 90 minutes after initial administration of 12.5 mg of Carvedilol and after 3 months of dose optimization. **Results:** Twenty-one (48.8%) patients demonstrated Acute Response and after dose optimization Chronic Response was seen in 29 (67.4%) patients with additional 8 (18.6%) patients responding to dose optimization. Fourteen (32.55%) patients failed to show any response. Low pre-drug Cardiac Output (CO), High pre-drug mean arterial pressure (MAP), more than 2.5mmHg drop in HVPG acutely, higher dose toleration of more than 18.5mg and lower change in HR predicted response. **Conclusion**: Patients with CTP Class A Cirrhosis with Portal Hypertension and Esophageal Varices tolerate Carvedilol well and nearly two-thirds show hemodynamic response when dose is optimized over a period of time, including patients who initially show no acute response. Nearly one-third of patients show no response even after dose optimization.

Key words: Carvedilol; hemodynamic study; acute response; chronic response; Mean Arterial Pressure (MAP); Cardiac output (CO); Chronic Liver Disease; Portal Hypertension; CTP Class

Access this article online

Website: http://nepjol.info/index.php/AJMS

DOI: 10.3126/ajms.v12i8.36500

E-ISSN: 2091-0576

P-ISSN: 2467-9100

INTRODUCTION

Development of esophageal varices and variceal bleeding are amongst the major Portal Hypertension related complications in patients with cirrhosis.[1] Standard of care in these patients pertain to use of Beta-Adrenergic Receptor Blockers (BB) and Endoscopic Variceal Ligation (EVL).[1-3] While EVL is the preferred modality for secondary prevention after first variceal bleed, both EVL and BB are equally effective in primary prevention, with

Address for Correspondence:
Dr. Shaheen Nazir Lone, Department of Gastroenterology, Superspeciality Hospital Shireen Bagh, Srinagar, India,1900011,
Email ID: anayahshaheen@gmail.com, **Mobile No:** +91-9797061298

the former preferred in patients with moderate to large varices, intolerance to Beta-Blockers or those who bleed while taking these medicines.[2-5]

BB additionally have survival benefits by reducing risk of Spontaneous Bacterial Peritonitis, HRS, ascites and are even suggested to decrease risk of Hepatocellular Carcinoma.[3,5] Whereas BB usage has been questioned especially in CTP C with refractory ascites, SBP and ACLF and data suggesting its benefit only in "therapeutic window" is still propagated, there is upcoming robust data against it.[1,6,7] It is contested that BB owing to their survival benefits should not be contraindicated but stopped only temporarily or dosage tapered in such scenarios.[5]

On the basis of hemodynamic studies, a direct correlation is found between Hepatic Venous Pressure Gradient (HVPG) and complications of Portal Hypertension; with a high likelihood of variceal bleeding associated with a HVPG of above 12 mmHg.[8,9] Reduction of HVPG by means of Beta-Blockers is a frontline strategy in prevention of variceal bleeds. Carvedilol with its combined Alpha and Beta blocking properties offers advantages even in patients not responding to NSBBs. Its antagonism of α1-receptors causes reduction in hepatic vascular resistance while by virtue of β-antagonism it modulates Cardiac output and Portal flow along with splanchnic vasoconstriction.[9,10] These combined actions produce a net effective reduction of Portal Pressures and hence the bleeding complications with efficacy better than that of Propranolol.[9-13] In addition, Carvedilol has shown survival benefit compared to EVL alone independent of reducing bleeding complications, likely by decreasing gut-congestion and reducing microbial translocation thereby decreasing the chances of SBP and infections.[14-16]

One of the main issues with Beta Blockers is their tendency to cause hypotension that remains a concern while optimizing therapy. Add on therapies are being studied that avoid hemodynamic side effects of beta-blockers while improving liver function through other mechanisms. Simvastatin owing to its anti-fibrotic effects along with its selectively increases bioavailability of NO in liver has encouraging results in Carvedilol non-responders.[17,18] This selectivity is unlike Organic Nitrates that additionally cause systemic Vasodilation and hence lead to hemodynamic perturbations and intolerance. Many other drugs, older as well as newer agents like Emricasan and Taurine are being studied in Portal Hypertension.[18]

Several hemodynamic studies to evaluate response to Carvedilol have been done in the past on patients having alcohol related cirrhosis[9,11,20,21] or viral[8,22] or both.[26] However, majority of them have not studied the response taking the stage of the disease (CTP Class) into consideration.[23] This is important as pathophysiology, hemodynamics and tolerance to drugs varies during the course of liver disease. Moreover, the factors responsible for lack of response have also not been studied in past, which could help us to determine a subset of patients who may need other modalities of treatment from the outset. In light of this we contemplated the present study to assess response selectively in CTP Class A and assess the factors associated with Non-Response.

MATERIAL AND METHODS

Our study was a hospital based prospective study conducted in the Department of Gastroenterology at a Tertiary Care Centre in North India. The study protocol was cleared by the Institutional Ethics Committee and written informed consent was taken from all participants**.** All consecutive patients of cirrhosis with CTP class A who consented for hemodynamic assessment from 2010 to 2013 were included in the study.

Inclusion criteria

Adults with

- Cirrhosis with CTP class A
- Esophageal Varices on Endoscopic gastroduodenoscopy (EGD)
- No past history of Malena or Hematemesis
- Baseline HVPG of more than 12mmHg

Exclusion criteria

- Age <18 years
- Non cirrhotic portal hypertension
- Cirrhosis with CTP class B and C
- Known malignancies/HCC
- Acute or Chronic kidney disease with creatinine more than >1.5mg/dl
- Active IV drug or Alcohol Abuser
- Liver Failure (INR more than 2.5 and bilirubin more than 5mg/dl)
- Severe systemic illness or sepsis
- Chronic pulmonary disease
- Psychiatric illness or lack of capacity to give informed consent
- Pregnant or lactating females
- Contraindications/allergies to Carvedilol use
- Patients already on any of portal hypertension lowering drugs, carvedilol or other BB or nitrate etc.

Cirrhosis was diagnosed on clinical, biochemical, radiological parameters and liver biopsy if so required. Ascites was defined on the basis of International ascites club 2003 as Grade I if picked up only on USG, grade II if

moderately symmetrical distension or grade III if grossly distended abdomen with ascites. Esophageal varices were defined by Bavino consensus as large or small if more or less than 5mm respectively.

HVPG measurement

- Under the fluoroscopic guidance hepatic vein catheterization was performed according to the standards outlined by Bosch et al. [10]
- Wedged hepatic venous pressure (WHP) was measured with help of 7F balloon tipped catheter advanced into right main hepatic vein.
- HVPG was determined by the difference of wedged and free hepatic pressures (WHVP – FHVP)
- Cardiopulmonary pressures, such as pulmonary artery pressure (PAP), wedged pulmonary pressure (WPP), and right atrial pressure (RAP) were measured with a Swan-Ganz catheter, advanced to the pulmonary artery.
- An automatic sphygmomanometer was used for noninvasive MAP measurement.
- Continuous ECG monitoring was used to calculate heart rate (HR).
- Systemic vascular resistance (SVR) was calculated from formula

$$SVR = MAP - RAP/CO \times 80.$$

Patients as per inclusion and exclusion criteria were enrolled. Baseline HVPG after 8 hours fast was measured. Baseline bilirubin, albumin, prothrombin time and International normalized ratio were checked. Carvedilol 12.5mg orally was given followed by repeat HVPG measurement at 90 minutes of intake. Acute response was defined as HVPG of less than 12mmHg and or 20% drop from baseline. After 24 hours carvedilol 6.25mg/day was started. Dose was increased @ 6.25mg/week till heart rate below 55 bpm and systolic blood pressure below 90 mmHg was achieved in compliant patients, which was checked at each visit. Patients were put on regular weekly follow up visits after optimization of dose. BP and HR were checked and side effects monitored and recorded at each follow up visit. HVPG and Baseline parameters were again measured after 3months of regular treatment. Chronic response which was defined as HVPG of less than 12mmHg and or 20% drop from baseline HVPG after treating with optimal dose of Carvedilol for 3 months

Statistical analysis

Statistical analysis was performed using a statistical software program SPSS version 20 (IBM). Continuous variables were expressed as mean and standard deviation (Mean (SD) and Range. Quantitative data between two groups was compared with the use of Student *t*-test for parametric data and Mann-Whitney U test for non-parametric data and Kruskal Wallis Test. Pearson chi-square test and Fisher's exact test were used for categorical data to see the association of variables. Odds ratio were used at appropriate places to see the strength of associations. All *P* values were two-tailed; *P* value of <0.05 was considered statistically significant. Chronic response was determined by analyzing univariate and multivariate logistic regression.

RESULTS

In this study 43 patients of Cirrhosis of different etiologies with CTP Class A were enrolled. Demographic features and baseline parameters are summarized in Table1 and etiologic distribution in Figure 1. The hemodynamic parameters are summarized in Table 2.

The acute response after stat dose of 12.5mg of carvedilol was achieved in 21 patients (48.8%). Mean baseline HVPG was 16.53 ± 2.06 mmHg which dropped to12.74 ± 2.46 mmHg after 90 min of carvedilol intake. Mean drop in HVPG in responders was 5.66 ± 1.46 mmHg compared to in 2.00 ± 0.53mmHg non-responders.

The factors which were found to be significantly related to acute response on univariate were low baseline CO, less change in HR and high MAP while on multivariate analysis low baseline CO was only independent predictor of acute response.

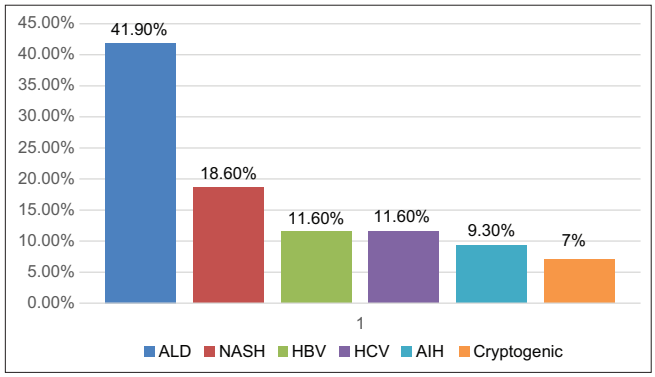

Figure 1: Etiological Distribution of Chronic liver disease

Table 1: Demographic features and Baseline parameters

Parameters	Description
Age in years Mean (SD)	57.26 (5.491)
Males/ Females	28 (65.1%) /15 (34.9%)
Esophageal varices (small: large)	23 (53.5%):20(46.5%)
Ascites	Grade 1 in one Patient
Serum Albumin(mg/dl)	3.69±0.29
Total Bilirubin(mg/dl)	1.150±.18
Prothrombin	12.721±.36
INR	1.160±0.08

Chronic response assessed after 3 months of optimized therapy was seen in 29(67.4%) patients thereby implying that 8(18.6%) of patients responded to increased dose as shown in Figure 2.

Mean Reduction in HVPG was 5. 517 ± 1.40 mmHg and 2.00 ± 0.55mmHg after three months in responders and non-responders respectively. None of our patients had any significant adverse event to merit discontinuation of therapy though two patients had minor side effects which resolved within few days.

Table 2: Hemodynamic parameters at Baseline, 90 minutes after Acute Administration of Carvedilol and at 3 months after dose optimization.

Parameter	Pre treatment Mean (SD)	Acute Post treatment Mean (SD)	Chronic Post treatmentb Mean (SD)	P value
CO (liter/min)	7.507 (0.1882)	6.493 (0.1710)	6.37 (0.15)	<0.001
HR (beats/min)	79.00 (2.628)	62.33 (2.212)	57.74 (2 .82)	<0.001
MAP (units)	89.30 (3.211)	78.49 (1.932)	75.79 (2.00)	<0.001
FHVP (mmHg)	8.37 (1.800)	9.58 (1.867)	9.63 (1.83)	<0.001
WHPG (mmHg)	24.86 (2.305)	22.30 (2.713)	21.70 (2.63)	<0.001
HVPG (mmHg)	16.53 (2.063)	12.74 (2.460)	12.16 (2.28)	<0.001

CO: Cardiac Output; HR: Heart Rate; MAP: Mean Arterial Pressure; FHVP: Free Hepatic Venous Pressure; WHPG: Wedged Hepatic Venous Pressure; HVPG: Hepatic Venous Pressure Gradient

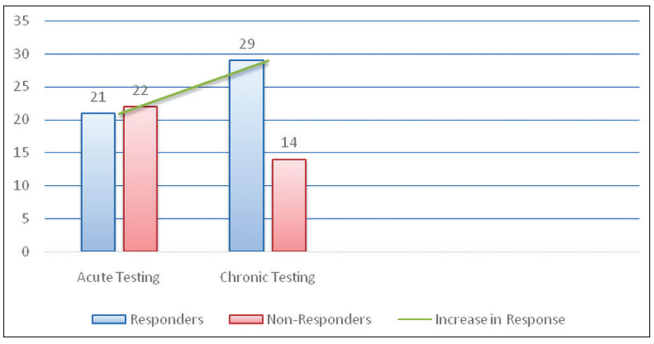

Figure 2: Hemodynamic response to Carvedilol

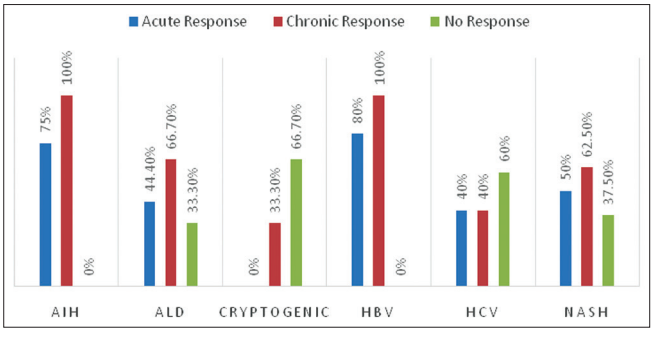

Figure 3: Etiology wise response rates to Carvedilol

Low baseline CO and more than 2.5 mmHg fall in HVPG during acute response predicted chronic response on Univariate analysis. On Multivariate analysis, more than 2.5 mmHg fall in HVPG during acute response were found as independent predictors of chronic response ($P < 0.05$).

Percentage of female responders was higher than that of males and with respect to etiology, response was slightly better in AIH and HBV but again both not statistically significant (Figure 3). Escalating the dose above 18.5mg and lesser decline in HR was found to be the predictors of chronic response with no acute response.

Dose was not statistically different for chronic response across different etiologies. Although it was not statistically significant, Mean dose of carvedilol was more among non-responders (23.85 ± 2.53 mg) as compared to responders 21.72 ± 3.85mg).

DISCUSSION

Patients of Chronic Liver Disease and Portal Hypertension are a heterogenous group with varied etiologies and progression of disease in various stages (CTP Classes). Pharmacotherapy is advantageous over invasive methods of managing portal hypertensive complications like EVL, sclerotherapy or Glue injections because of its overall systemic effects to correct hemodynamic derangements.[5]

Though hemodynamic studies are not technically and logistically feasible in every patient, they are the only direct way to assess response to pharmacotherapy. Notwithstanding this limitation, a number of hemodynamic studies have been conducted on response assessment and tolerability including two by our own group.[16,23-25]

In the present study forty-three patients with CTP Class A were enrolled and, on the basis of response to Carvedilol, different groups were identified –

1. No Response i.e., neither acute nor chronic (NR)
2. Chronic Response (CR)

The Chronic Responders further included two subtypes:

a) Acute Response and maintained it in Chronic Phase (ARCR)
b) No Acute Response but Chronic Response (CRNAR) after dose optimization.

Twenty-one (48.8%) demonstrated AR to oral loading of Carvedilol with nearly half of the patients having

no response during initial hemodynamic assessment. Many studies have been done to investigate acute effects of carvedilol individually and comparing it with propranolol or combination therapies and previous studies have demonstrated response rates between 40 to 70%. [9, 12, 22] The variations in response may be due to different selection criteria in the studies, definition of response, heterogeneity of the study population, etiology of the disease or different doses of Carvedilol used. In one of the earliest hemodynamic study Forrest et al. [11] used 25mg of Carvedilol, that is twice as we used in our study and defined response as more than 10% decrease in portal pressure as compared to 20% by our group, therefore for apparent reason response was noted in 81%, much more as compared to one-half in ours. There after more studies with similar dose[9,12,21,22] or lower doses, 10-12.5mg[20, 26] were conducted and all showed significant reduction in portal pressures more or less comparable to our results if other confounding factors are taken in to account.

On univariate analysis low Cardiac Output (CO), high Mean Arterial Pressure (MAP) and Minimal change in Heart Rate (HR) proved to be statistically significant predicting factor for achieving acute response. On multivariate analyses lower CO was found to be independent predictor of acute response ($P < 0.05$). MAP has been found to be independent predictor of survival in studies in past.[19] The low baseline Cardiac Output as predictor of response is interesting as it might suggest improved Cardiac Performance with Carvedilol over a period of time leading to improved Cardiac Output and low systemic venous congestion that translates to lower portal pressures. Also, relation of responsiveness to less change in heart rate could be due to better tolerance of drug leading to dose escalation. These are however only hypothesis that needs further elucidation and investigation.

To assess Chronic Response, hemodynamic parameters were repeated after 3 months of optimization of Carvedilol therapy. Twenty nine out of 43 (67.4%) patients demonstrated chronic response, compared to only 48.8% who had acute response thereby proving that there is a subset of patients who will respond to optimized chronic therapy even though not responding to initial loading. Chronic Effects of Carvedilol on Portal Pressures have been assessed in many studies[12,20,22,27] The overall Chronic Response rate of 67.4% in our study corresponds well to previously reported data in literature[22,27,28] Rabergius et al. found 56% hemodynamic response with Carvedilol even in Propranolol non-responders, with significant decline in HVPG than propranolol.[27] Their results demonstrated that with carvedilol use not only a greater number of patients achieve a hemodynamic response, but is associated with lesser decompensation and improved survival. Banares R et al. showed that 54% of patients achieved significant chronic response with more decrease in HVPG and MAP but may have more adverse effects due to hypotension caused by Carvedilol.[28] Similar results were reported by Binay K De et al. who also found that acute HVPG reduction correlated with response after chronic ingestion.[22] Factors that envisaged Chronic Response on Univariate analysis were low baseline CO and more than 2.5 mmHg fall in HVPG during acute response. The latter was found to be an independent predictor of Chronic Response on Multivariate analysis ($P < 0.05$).

There were 8(18.6) patients who initially had no Acute Response, but showed Chronic Response (CRNAR) after dose optimization at 3 months. Our strategy of starting with a lower dose and up-titrating as per clinical variables is physiologically appropriate given that the cardiovascular tolerance of Carvedilol develops gradually. Previous studies which started with high initial doses had more dropout cases and dose reductions due to unfavorable side effects of the drug. [12] In our study only two patients reported minor side effects and none of our patients needed discontinuation of treatment due to side effects. Mean titrated dose for Responders and Non-responders at 3 months was 21.72 ± 3.84 and 23.85 ± 2.53 mg respectively. Mean dose being slightly lesser for Responders than Non-responders may point to the fact that dose response correlation plateaus above a certain limit. Higher tolerated dose of Carvedilol 18.5 mg or more and low HR change were found to be significantly associated with chronic response on no acute response ($P < 0.05$). This again proves that factors predicting better tolerance would predict better response.

Despite dose titration and no adverse effects, 14 (32.6%) patients neither responded acutely nor after regular three months of treatment (NR). In our study we didn't find any clinical, etiologic, demographic or laboratory factor that were statistically different between responders and non-responders. It is not uncommon clinical scenario to see patients put on blanket beta-blocker treatment, persisting to have high grade varices or presenting with bleed on follow up. For non-responders we may need to use add on or different therapies, preferably drugs not having hypotensive effects such as statins that act by their anti-inflammatory and antifibrotic mechanisms. The sequential treatment approach with addition of statins in non-responders improved response rates from around 60% to 80% shown by our group in past.[17] Simvastatin increases the intrahepatic bioavailability of NO thereby decreasing both hepatic resistance and splanchnic congestion consequently improving central blood volume.[17,18] Other statins like rosuvastatin and pravastatin also have been found effective and safe in liver disease. There are many

more drugs in pipeline which are being studied and can be used as add on therapy.[17, 18]

Advantage of our methodology is that we enrolled patients of only CTP Class A, making study group more homogenous. We started with smaller tolerable dose and gradually optimized it to improve tolerance and avoid adverse hemodynamic effects. We assessed both acute and chronic responses and also determined maximum tolerable dose. Though one of our aims was to identify clinical variables that could help in predicting non-responders, there was none statistically significant. The latter could have been due to smaller sample size of our study and for a definite answer a bigger study is needed to better clarify the same.

CONCLUSION

This study highlights that patients with CTP Class A tolerate Carvedilol well without much side effects, giving us more liberty to escalate to higher doses, which is limited in CTP Classes B and C. Starting with a lower dose and titrating up improves response rates with improved tolerance and minimizes dropouts. Acute responders maintain the response over period of time and in fact initial response is important predictor of chronic response. Nearly one-fifth of patients who do not show Acute Response will show Chronic Response after dose optimization, improving the rate of Chronic Responders compared of Acute Responders. One third of patients don't respond even after dose optimization, and predicting the lack of response would help to switch over these patients to other form of treatment or combination therapy.

Recommendation

Further studies are required to study the factors associated with Non-Response along with assessing the efficacy and feasibility of Carvedilol in all Child Class categories separately. Additionally, studies are required to elucidate early identification and optimal management in Non-Responders who may benefit from upfront interventional therapy or alternative pharmacological management.

REFERENCES

1. Krag A, Wiest R, Albillos A and Gluud LL. The window hypothesis: haemodynamic and non-haemodynamic effects of β-blockers improve survival of patients with cirrhosis during a window in the disease. Gut 2012; 61:967-969.
   https://doi.org/10.1136/gutjnl-2011-301348
2. Drastich P, Lata J, Petrtyl J, Bruha R, Prochazka V, Vanasek T, et al. Endoscopic variceal band ligation compared with propranolol for prophylaxis of first variceal bleeding. Ann Hepatol.2011; 10:142-149.
   https://doi.org/10.1016/S1665-2681(19)31562-5
3. Rodrigues SG, Mendoza YP and Bosch J. Beta-blockers in cirrhosis: evidence-based indications and limitations. JHEP Rep. 2019; 2:100063.
   https://doi.org/10.1016/j.jhepr.2019.12.001
4. Shah HA, Azam Z, Rauf J, Prakash O, Subhan A and Munir SM. Carvedilol vs. esophageal variceal band ligation in the primary prophylaxis of variceal hemorrhage: a multicentre randomized controlled trial. J Hepatol. 2014; 60(4):757-764.
   https://doi.org/10.1016/j.jhep.2013.11.019
5. Rodrigues SG, Mendoza YP and Bosch J. Beta-Blockers in Cirrhosis: Evidence - based indications and limitations. JHEP Reports. 2020; vol.2/100063.
   https://doi.org/10.1016/j.jhepr.2019.12.001
6. Serste T, Melot C, Francoz C, Durand F, Rautou PE, Valla D, et al. Deleterious effects of beta-blockers on survival in patients with cirrhosis and refractory ascites. Hepatology. 2010; 52:1017-1022.
   https://doi.org/10.1002/hep.23775
7. Krag A, Bendtsen F, Henriksen JH and Moller S. Low cardiac output predicts development of hepatorenal syndrome and survival in patients with cirrhosis and ascites. Gut. 2010; 59:105-110.
   https://doi.org/10.1136/gut.2009.180570
8. Lin HC, Yang YY, Hou MC, Huang YT, Lee FY and 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.
   https://doi.org/10.1111/j.1572-0241.2004.40179.x
9. Bañares R, Moitinho E, Piqueras B, Casado M, Garcia-Pagan JC, de Diego A and Bosch J. Carvedilol, a new nonselective beta-blocker with intrinsic anti-Alpha1-adrenergic activity, has a greater portal hypotensive effect than propranolol in patients with cirrhosis. Hepatology.1999; 30:79-83.
   https://doi.org/10.1002/hep.510300124
10. Bosch J. Carvedilol for portal hypertension in patients with cirrhosis. Hepatology.2010; 51:2214-2218.
    https://doi.org/10.1002/hep.23689
11. Forrest EH, Bouchier IA and Hayes PC. Acute haemodynamic changes after oral carvedilol, a vasodilating beta-blocker, in patients with cirrhosis. J Hepatol.1996; 25:909-915.
    https://doi.org/10.1016/S0168-8278(96)80296-0
12. Stanley AJ, Therapondos G, Helmy A and Hayes PC. Acute and chronic haemodynamic and renal effects of carvedilol in patients with cirrhosis. J Hepatol.1999; 30:479-484.
    https://doi.org/10.1016/S0168-8278(99)80108-1
13. 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 haemodynamic non-response to propranolol. Gut.2013; 62:1634-1641.
    https://doi.org/10.1136/gutjnl-2012-304038
14. Villanueva C, Albillos A, Genescà J, Garcia-Pagan JC, Calleja J L, Aracil C, et al. β blockers to prevent decompensation of cirrhosis in patients with clinically significant portal hypertension (PREDESCI): a randomised, double-blind, placebo-controlled, multicentre trial. Lancet. 2019; 393:1597-608.
    https://doi.org/10.1016/S0140-6736(18)31875-0
15. Leithead JA, Rajoriya N, Tehami N, Hodson J, Gunson BK, Tripathi D, et al. Non-selective β-blockers are associated with improved survival in patients with ascites listed for liver transplantation. Gut.2015; 64:1111-1119.
    https://doi.org/10.1136/gutjnl-2013-306502

16. McDowell HR, Chuah CS, Tripathi D, Stanley AJ, Forrest EH and Hayes PC. Carvedilol is associated with improved survival in patients with cirrhosis: a long-term follow-up study. Aliment Pharmacol Ther. 2021;53(4):531-539.
17. Wani ZA, Mohapatra S, Khan AA, Mohapatra A and Yatoo GN. Addition of simvastatin to carvedilol non responders: a new pharmacological therapy for treatment of portal hypertension. World J Hepatol. 2017; 9(5):270-277.
https://doi.org/10.4254/wjh.v9.i5.270
18. Pose E, Trebicka J, Mookerjee RP, Angeli P and Gines P. Statins: old drugs as new therapy for liver diseases? J Hepatol. 2019; 70(1):194-202.
https://doi.org/10.1016/j.jhep.2018.07.019
19. Llach J, Gines P, Arroyo V, Rimola A, Tito L, Badalamenti S, et al. Prognostic value of arterial pressure, endogenous vasoactive systems, and renal function in cirrhotic patients admitted to the hospital for the treatment of ascites. Gastroenterology. 1988; 94:482-487.
https://doi.org/10.1016/0016-5085(88)90441-6
20. Tripathi D, Therapondos G, Lui HF, Stanley AJ and Hayes PC. Hemodynamic effects of acute and chronic administration of low-dose carvedilol, a vasodilating betablocker, in patients with cirrhosis and portal hypertension. Aliment Pharmacol Ther.2002; 16:373-380.
https://doi.org/10.1046/j.1365-2036.2002.01190.x
21. Silkauskaite V, Pranculis A, Kupcinskas J, Petrenkiene V and 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.
https://doi.org/10.1016/S0168-8278(09)60228-2
22. De BK, Das D, Sen S, Biswas PK, MandalSK, Majumdar D, et al. Acute and 7-dayportal pressure response to carvedilol and propranolol in cirrhotics. J Gastroenterol Hepatol. 2002; 17:183-189.
https://doi.org/10.1046/j.1440-1746.2002.02674.x
23. Malandris K, Paschos P, Katsoula A, Manolopoulos A, Andreadis P, Sarigianni M, et al. Carvedilol for prevention of variceal bleeding: a systematic review and meta-analysis. Ann Gastroenterol 2019; 32 (3): 287-297.
https://doi.org/10.20524/aog.2019.0368
24. Wani ZA, Bhat RA, Bhadori AS, Zargar SA, Shah AH, Maiwall R, et al. A Haemodynamic Analysis to Assess the Safe Dose of Carvedilol across Different Child Class of Liver Disease. BJMMR. 2015; 7: 355-368.
https://doi.org/10.9734/BJMMR/2015/15398
25. Wani ZA, Baht RA, Bhadoria AS, Maiwall R, Majeed Y, Khan AA, et al. 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? Saudi J Gastroenterol. 2015; 21: 278-283.
https://doi.org/10.4103/1319-3767.164207
26. 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. Arzneimittelforschung.1997; 47:353-355.
27. 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.
https://doi.org/10.1136/gutjnl-2012-304038
28. Bañares R, Moitinho E, Matilla A, García-Pagán JC, Lampreave JL, Piera C, et al.Randomized comparison of long-term carvedilol and propranolol administration in the treatment of portal hypertension in cirrhosis. Hepatology.2002; 36:1367-1373.
https://doi.org/10.1002/hep.1840360612

Authors Contribution:
ZA- Conceived concept and design of the study, proposed the first draft of manuscript; **SN-** Interpreted the results, reviewed the literature, edited and prepared final manuscript; **IUH-** performed the statistical analysis; **WA, MM, AA, AH-** managed the experimental and review process

Work attributed to:
Sher- i -Kashmir Institute of Medical Sciences, Srinagar, Jammu and Kashmir, India

Orcid ID:
Dr. Shaheen Nazir- https://orcid.org/0000-0002-6550-8724
Dr. Zeeshan Ahmed- https://orcid.org/0000-0002-1096-2874
Dr. Muzzafer Mohamad- https://orcid.org/0000-0002-0412-4364
Dr. Afaq Ahmad- https://orcid.org/0000-0001-5931-4969
Dr. Wasim Ahmed- https://orcid.org/0000-0002-6008-7123
Dr. Inaam-ul-Haq- https://orcid.org/0000-0001-8559-8010
Dr. Altaf Hussain- https://orcid.org/0000-0002-1723-6322

Source of Support: Nil, **Conflict of Interest:** None declared.