Long-term hemodynamic response of carvedilol and simvastatin in compensated versus decompensated chronic liver disease with portal hypertension

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ABSTRACT

Background: A combination of carvedilol and Simvastatin have recognized their role as rescue therapy for carvedilol non-responders in chronic liver disease (CLD)-associated portal hypertension. However, there are scarce data regarding its role in specific subclasses, and stratification of response according to the computed tomographic perfusion (CTP) score has never been seen before. **Aims and Objective:** (1) To compare hemodynamic response and side effects of a combination therapy in decompensated and compensated patients. (2) Stratify the effect of combination therapy according to CTP score. **Materials and Methods:** In 102 consecutive patients of CLD with esophageal varices, the hepatic venous pressure gradient was measured at baseline and after 3 months of dose optimization of carvedilol. Simvastatin was added to non-responders and hemodynamics repeated at 1 month of dual therapy. The response of compensated CLD was compared with decompensated patients and was stratified as per the CTP on follow-up. **Results:** Overall, out of 43 compensated patients, 21 responded acutely and response increased to 29 (67.44%) at 3 months. While 31 of 59 (52.54%) decompensated patients responded acutely but dose escalation did not increase response significantly after 3 months. The addition of Simvastatin did increase the response, although side effects were more in decompensated group. The addition of Simvastatin also decreased decompensation in the high-risk compensated group and maintained their MELD. Na. **Conclusion:** Response in compensated CLD patients was more than in decompensated patients; however, it was statistically insignificant. Attrition was more in patients with CTP > 10 due to drug intolerance, side effects, or deaths.

Key words: Simvastatin; Carvedilol; Hemodynamic study; Chronic liver disease; Decompensated; Compensated

INTRODUCTION

The progression of chronic liver disease (CLD) is assessed by numerous methods, and many scoring systems have been developed to assess the severity of the disease. Various benchmarks have been set, beyond which medical therapy may not be beneficial and mortality will be high if not intervened. As CLD advances and the patient decompensates, hemodynamic parameters change noticeably. The rate of development of varices doubles as Hepatic venous pressure gradient (HVPG) rises above 10 mmHg, and the probability of bleeding increases as the HVPG rises above 12 mmHg.[1] Therefore, hemodynamic response correlates well with the clinical response when anti-portal hypertensive drugs are used to target HVPG.[2] Hemodynamic studies are not feasible in routine clinical practice, and correlating hemodynamic

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derangements with the commonly used clinical scores may make it more practical. MELD score and computed tomographic perfusion (CTP) class are the most commonly used score in the clinical practice.

Endoscopic variceal ligation (EVL) and beta-adrenergic receptor blockers (BB) are almost equally efficacious for primary prophylaxis of variceal bleeding except if varices are moderate to large, the patient is intolerant to beta-blockers or bleeds while on BB, where former has an edge over pharmacotherapy.[3] Moreover, BBs, due to their systemic effects, improve overall survival by decreasing the chances of complications such as spontaneous bacterial peritonitis, hepatorenal syndrome, and even hepatocellular carcinoma (HCC).[3] Thus, notwithstanding some controversies regarding their usage in the early and late stages of liver disease, BB is the standard of care treatment modality for CLD across all stages.[3]

Only 2/5th of patients respond to nonselective BBs in portal hypertension, which increases to not more than 60% even after using more potent BB like carvedilol having combined alpha and beta receptor blocking properties.[4] Add-on therapy is consequently still needed in around two-fifth of patients, so many have been explored and are in the pipeline. Statin has ideal add-on therapy properties to BB non-responders, with no effect on mean arterial pressure (MAP) or peripheral vascular resistance, can improve liver function, and is a liver-selective vasodilator.[5]

We proved the effectiveness of Simvastatin in the treatment of portal hypertension in our previous studies[6] but how its efficacy and safety profile vary in compensated and decompensated patients needs to be studied further. We may have to modify and tailor-make the options based on the clinical scenario. A preemptive decision to continue or stop medical treatment in decompensated patients and stratification based on CTP may be needed to avoid a precipitous increase in portal pressures in emergent situations where pharmacotherapy needs to be withdrawn to avoid side effects. These patients usually come with refractory variceal bleeds and even post-EVL ulcer bleeds. It becomes imperative to select the patients judicially for preemptive EVL so that we cost-effectively prevent these situations. We contemplated this study to stratify the response based on CTP which is the most widely used staging so that the above situation can be avoided.

Aims and objectives
The purpose of this study was

1. To evaluate the hemodynamic response of a combination of Simvastatin and Carvedilol in decompensated Cirrhosis as compared to compensated patients.

2. To stratify the effect of combination therapy on patients according to CTP score.
3. To see the side effect profile

MATERIALS 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 significant portal hypertension who consented to hemodynamic assessment from 2010 to 2013 were included in the study and were followed for 2 years.

Inclusion Criteria
Adults with
- Cirrhosis
- Esophageal varices on endoscopic gastroduodenoscopy
- No history of Malena or hematemesis
- Baseline HVPG of more than 12 mmHg

Exclusion criteria
- Age <18 years
- Non-cirrhotic portal hypertension
- Known malignancies/HCC
- Acute or chronic kidney disease with a creatinine of more than >1.5 mg/dl
- Active IV drug or alcohol abuser
- Liver failure (INR more than 2.5 and bilirubin more than 5 mg/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/simvastatin use
- Patients already on any of the portal hypertension lowering drugs, carvedilol or other BB or nitrate, etc.

Cirrhosis was diagnosed on clinical, biochemical, and radiological parameters, and liver biopsy if so required. Ascites was defined based on the International Ascites Club 2003 as Grade I if picked up only on ultrasonography, grade II if moderately symmetrical distension, or Grade III if grossly distended abdomen with ascites. Esophageal varices were defined by Baveno consensus as large or small if more or less than 5 mm, respectively.

Compensated cirrhosis (with or without varices) and decompensated cirrhosis (presence of ascites or varices with bleed) were defined per the Baveno consensus conference.

HVPG measurement

- Under fluoroscopic guidance, hepatic vein catheterization was performed according to the standards outlined by Bosch et al.[4]
- Wedged hepatic venous pressure (WHVP) was measured with the help of a 7F balloon-tipped catheter advanced into the right main hepatic vein.
- HVPG was determined by the difference between wedged and free hepatic pressures (WHVP – free hepatic venous pressure)
- Cardiopulmonary pressures, such as pulmonary artery pressure, wedged pulmonary pressure, 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 the formula.

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

Patients, as per inclusion and exclusion criteria, were enrolled. Baseline HVPG after 8 h of fast was measured. Baseline bilirubin, albumin, prothrombin time, and International normalized ratio were checked. Carvedilol 12.5 mg orally was given followed by repeat HVPG measurement at 90 min of intake. The acute response was defined as HVPG of less than 12 mmHg and or 20% drop from baseline. After 24 h carvedilol 6.25 mg/day was started. The dose was increased @ 6.25 mg/week till a HR 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 the optimization of the dose. BP and HR were checked, and side effects were monitored and recorded at each follow-up visit. HVPG and baseline parameters were again measured after 3 months of regular treatment. The chronic response, which was defined as HVPG of <12 mmHg and or 20% drop from baseline HVPG after treatment with an optimal dose of carvedilol for 3 months, was checked. Simvastatin 20 mg/d for 15 days (then increased to 40 mg) was added in carvedilol non-responders. Complete clinical examination and blood tests were performed on day 15, and patients were interrogated specifically for muscle weakness, if no side effect was seen, the dose was increased to 40 mg/day and continued in addition to carvedilol. The combination was continued for 1 month, and then repeat hemodynamic response was measured. Treatment was continued for 2 years in responders to combination pharmacotherapy, and the hemodynamic response was measured again at 2-year follow-up. Response in decompensated versus compensated CLD was compared. CTP score was calculated, and the response was stratified according to the CTP score.

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 the two groups were compared with the use of the Student *t*-test for parametric data and Mann–Whitney U test for non-parametric data, and the Kruskal–Wallis Test. Pearson Chi-square test and Fisher's exact test were used for categorical data to see the association of variables. Odds ratios were used at appropriate places to see the strength of associations. All P-values were two-tailed; a $P < 0.05$ was considered statistically significant. The chronic response was determined by analyzing univariate and multivariate logistic regression.

RESULTS

Two hundred patients of CLD of varied aetiologies with clinically significant portal hypertension (CSPH) in form varices and baseline HVPG of more than 12 mmHg were enrolled as per the inclusion and exclusion criteria. Out of these, 43 patients had compensated CLD, and 59 patients had decompensated CLD. Sixty-three (61.85%) were male, and 39 (38.2%) were female patients with a mean age of 58.35±6.62 years. Demographic features and baseline parameters are summarized in Table 1.

Mean pre-drug HVPG was 16.75±2.12 mmHg, which dropped to 12.74±2.460 mmHg and 13.31±207 after 90 min of administration of 12.5 mg of carvedilol in compensated and decompensated CLD, respectively. The mean drop of HVPG was 4.5±2.2 mmHg and 2.4±1.9 mmHg among responders and nonresponders, respectively. Overall 21 patients (48.8%) showed an acute response, i.e., <12 mmHg or 20% drop in HVPG from baseline in compensated and 31 (52.5%) in decompensated patients. Mean (±SD) hemodynamic parameters for predrug and postdrug are shown in Table 2.

Table 1: Demographic features and baseline parameters

Parameters	Description, n=102
Age in years mean (SD)	58.35±6.62
Males/females	63:39
Compensated/decompensated	43:59
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

SD: Standard deviation

Table 2: Predrug and postdrug hemodynamic parameters

Hemodynamic parameters	Baseline in compensated cirrhosis	Postchronic carvedilol (3 mo in compensated cirrhosis)	Baseline in decompensated cirrhosis	Postchronic carvedilol (3 mo in decompensated cirrhosis)
CO (L/min)	7.507±0.188	6.49±0.17	7.539±0.197	6.508± 0.271
HR (beats/min)	79.00± 2.628	62.33±2.212	79.78± 2.371	60.83±1.849
MAP (mmHg)	89.30±3.21	78.49±1.932	89.69±1.643	77.68±1.746
FHVP (mmHg)	8.37±1.800	9.58±1.876	8.22±1.903	9.36±1.945
WHPG (mmHg)	24.00±2.305	22.30±2.713	25.24±2.725	23.14±2.453
HVPG (mmHg)	16.53±2.063	12.74±2.460	16.92±2.168	13.31±2.207

HR: Heart rate, MAP: Mean arterial pressure, FHVP: Free hepatic venous pressure, WHPG: Wedged hepatic venous pressure, HVPG: Hepatic venous-portal gradient

After 3 months of optimization of dose-response increased to 67.4% in compensated patients and 55.9% in decompensated patients. On further subgroup analysis and stratification with CTP score, no acute non-responder above CTP 10 benefited from dose escalation. All acute responders maintained their response, but one patient above CTP 10 lost the response and two could not tolerate the dose escalation. Adverse effect in the form of hypotension, leading to discontinuation of treatment, was seen in 2 patients, both from the decompensated group. Among nine who had mild side effects, seven were from the decompensated group. Simvastatin 20 mg/day was added initially for 15 days and then increased to 40 mg/day for chronic non-responders, after ensuring there were no clinical or biochemical adverse effects like muscle weakness or liver and muscle enzyme elevation.

Out of 38 patients, three patients were withdrawn due to adverse effects; one had Hepatic Encephalopathy, one had severe dizziness, and one had CPK >5 times with normal ALT. Four had minor side effects which improved and did not merit discontinuation of treatment. All seven of these patients had a decompensated disease, while compensated patients tolerated the drug well. Thirty-five patients continued combination pharmacotherapy for a month and then a repeat hemodynamic assessment was done. There were 16 responders (45.57%) after adding simvastatin, thereby increasing the overall response rate to 76.47% amongst compensated and 69.49% in decompensated patients.

Out of decompensated patients, one patient underwent a liver transplant, one died, and one was lost to follow-up. At 2 months' post simvastatin treatment, the mean MELD-Na was as15.076±3.707 while at follow-up of 2 years post simvastatin therapy, the mean MELD-Na was 17.076±4.9067. Since mean MELD-Na did not worsen significantly, implicating the role of statins in preventing decompensation in the high-risk compensated group. Although patients had trivial side effects, which resolved within a few days, none needed discontinuation of therapy.

DISCUSSION

It is well known by now that HVPG is almost a surrogate marker for the progression and complications of patients with CLD.[2] Hemodynamic studies are the only direct means to assess response to pharmacological agents. Numerous hemodynamic studies have been conducted; nonetheless, they are not feasible for clinical use routinely.[7] Anti-portal hypertensive drugs are favored for the prevention of variceal bleeding due to their mortality benefits, owing to their systemic effects in addition to reducing HVPG. Carvedilol has been established as a more effective and well-tolerated substitute, but still 2/5th do not respond.[4] After a certain dose, hypotension and bradycardia develop, necessitating add-on or alternative therapies. Simvastatin has proven to be ideal salvage therapy owing to its pleiotropic effects and reassuring results in carvedilol nonresponders.[6,8] There is ample data in favor of statins as an anti-portal hypertensive drug, but data showing its role in decompensated CLD is scarce. Hemodynamic response to anti-portal hypertensive drugs assessed by targeting HVPG correlates well with clinical response.[7] HVPG measurement is cumbersome and cannot be done in routine clinical practice. The prognostic value of the HVPG at each step in association with other standard predictive factors, such as CTP class is important as these scorings are more practical in routine clinical practice. Therefore, correlating hemodynamic derangements with clinical scores may make it more appropriate and pertinent.

Simvastatin and carvedilol combination has proven to be efficacious for the treatment of portal hypertension and increases the hemodynamic response from 60% to 80% as seen in previous literature.[6] Bishnu et al., verified superior response with an additional decline in HVPG by combined therapy of statins and beta-blockers.[9] Nonetheless, its effectiveness and safety profile differ in compensated and decompensated patients. The median survival compensated patients is around 12 years, while decompensated patients are expected to survive <2 years.[10,11] Since it has also been seen that both stages have different predictors of death,[10] therefore, by consensus, compensated and decompensated

cirrhosis should be considered distinct disease entities.[12] Therefore, it seems relevant to compare treatment responses separately in these two groups. In the present study, out of 100 and two patients 43 had compensated disease while fifty-seven had decompensated disease. Initially, 48.8% and 52.5% responded to stat dose of carvedilol in the former and latter groups, respectively. After the optimization of treatment over 3 months, the response in these groups was 67.4% and 55.9%, correspondingly. Overall response decreased, and patients did not respond to optimized doses of carvedilol after CTP 10. Out of 38 patients of carvedilol non-responders, 14 had compensated cirrhosis, and 24 had decompensated disease. The addition of simvastatin in non-responders over 1 month increased hemodynamic response in compensated and decompensated disease to 8 (61.5%) and 8 (36.36%) patients, respectively. Three patients, one in compensated and two in decompensated patients, were lost to follow-up.

Transition to a decompensated stage is marked by the development of variceal bleeding, ascites, encephalopathy, or jaundice.[10,11] None of our compensated CLD decompensated during a follow-up period of two years. Statins were found to decrease chances of decompensation in high-risk compensated patients but not tolerated well in decompensated patients, as seen in previous studies as well.

CSPH is defined as a HVPG $\geq$10 mmHg and is more likely to decompensate while patients without CSPH have a 90% event-free survival over 4 years.[13] Patients with CSPH but without esophageal varices develop decompensation at a rate of 7–10%/year.[13] Patients with CSPH and varices that have not bled are at 19% risk of decompensation and a 5% risk of death over 2 years.[13] Even though all our patients were high-risk compensated patients with esophageal varices and HVPG above 10 mmHg. None of our patients bled implying a decrease in the incidence of variceal bleeding, as shown in previous studies.[6,8,9] None of our high-risk compensated patients decompensated during the treatment course and follow-up of 2 years. Only one patient died during the follow-up thus stressing mortality benefits as well. Five patients with decompensated CLD and 8 with compensated CLD were followed for two years. At 2 months post simvastatin treatment mean MELD-Na was as 15.076±3.707 while at follow-up of 2 years post simvastatin therapy, the mean MELD-Na was 17.076±4.9067. Hence, MELD-Na stabilized, and the reduction in HVPG was sustained at 2 years. This suggests that statins improve survival and prevent decompensation if compared to the natural history of cirrhosis.[10-12]

Supported by data from the veteran affairs clinical case registry, the use of statins within patients with hepatitis C virus (HCV) and compensated cirrhosis is related to a 40% or higher reduction in the risk of cirrhosis decompensation and death.[14] Huang et al.,[15] showed that patients with chronic hepatitis B who received statin had a dose-dependent reduction in the risk of cirrhosis complications. Statins, in a dose-dependent manner, decrease the decompensation rate in both HBV- and HCV-related cirrhosis.[16] Kumar et al.,[17] demonstrated that statins delay cirrhosis complications and reduce mortality. Statins reduced the risk of decompensation and death in all studies.[18] When its efficacy was stratified over CTP score, there was a major change beyond CTP 10. The response was less in decompensated patients beyond CTP 10 though not statistically significant.

As CTP increases more than 10 side effects were more. Attrition was more in patients with CTP < 10 due to drug intolerance, side effects, or deaths. Three patients needed withdrawal of treatment due to side effects in the decompensated group but none in the decompensated group. Smaller doses of both carvedilol and simvastatin should be used in patients with higher CTP so that they get the mortality benefit of systemic therapy and yet avoid side effects.

It raised concerns regarding the safety of simvastatin when rhabdomyolysis was seen in two out of 69 patients on simvastatin (2.9%), compared to incidence of 0.009% to 0.1% in the general population, in bleeding prevention with simvastatin trial which evaluated the addition of simvastatin to standard therapy for preventing variceal rebleeding.[8] The authors observed that both patients had a more advanced liver disease with bilirubin levels >5 mg/dL. Consequently, Abraldes et al.,[5] concluded that severely worsened liver function patients might develop muscle injury at lower doses than the general population.

We recommend that preemptive EVL should be done in patients with CTP of more than 10 so that we may avoid a precipitous increase in portal pressures leading to refractory variceal bleeds and even post-EVL ulcer bleeds with high mortality in emergent situations like acute decompensation or ACLF when BBs usually need to be withdrawn.

Liver function tests and CPK were checked after every month as well as 2 monthly questionnaires for muscle weakness after the first assessment on the 15th and 30th day of initial treatment was done. Three patients who were excluded from the study due to side effects had CTP more than 10. Four patients had minor side effects that resolved without discontinuing treatment.

Our study is the one of the earliest studies which followed patients on sequential treatment for a longer period and compared compensated with decompensated patients.

Recommendation

Pharmacotherapy provides systemic survival benefits in addition to anti-portal hypertensive effects, but not all patients respond even to combination therapy. Management of the Decompensation of CLD poses a major challenge to clinicians, and a higher CTP score is one of the predictors of non-response and severe adverse effects. Data available till now are in small numbers and mostly retrospective. Larger studies to compare the clinical or hemodynamic response in compensated and decompensated patients are needed to further validate our results.

Limitations of the study

The limitation of our study is the small number of patients on combination therapy, thus necessitating further study in large-scale trials. More homogeneous study groups with larger sample size is needed to avoid confounding factors effecting the results.

CONCLUSION

Simvastatin and Carvedilol-based combination rescue therapy in Carvedilol non-responders is a promising approach. Compensated liver disease patients tolerate it better and have fewer safety concerns. This study showed the beneficial effects of this combination of pharmacotherapy as primary prophylaxis in compensated cirrhosis, but in patients of decompensated cirrhosis with CTP more than 10, upfront banding may be a more practical option than pharmacotherapy. Rescue therapy in addition to preventing variceal bleeding decreased decompensation in the high-risk compensated group and maintained their MELD. Na.

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