Hemodynamic Response to Carvedilol is Maintained for Long Periods and Leads to Better Clinical Outcome in Cirrhosis: A Prospective Study

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Background: **Non-selective beta-blockers (NSBBs), e.g. propranolol, are recommended for prophylaxis of variceal bleeding in cirrhosis. Carvedilol, a newer NSBB with additional anti-α1-adrenergic activity, is superior to propranolol in reducing portal pressure. Repeated HVPG measurements are required to identify responders to NSBB. We aimed to determine whether a single-time HVPG measurement, using acute-hemodynamic-response-testing, is sufficient to predict long-term response to carvedilol, and whether these responders have better clinical outcome.** ***Methods:*** **Consecutive patients with cirrhosis, aged 18–70 years, in whom NSBB was indicated for primary/secondary prophylaxis of variceal bleeding, and who underwent HVPG were included. Acute-hemodynamic-response was defined as a decrease in HVPG ≥10% from baseline or absolute HVPG value declining to <12 mm Hg, 1 h after 25 mg oral carvedilol. The aims of the study were to determine: the proportion of patients who achieved acute-hemodynamic-response to carvedilol; whether HVPG-response is maintained for 6 months; and clinical outcome of acute-responders to carvedilol therapy for 6 months.** ***Results:*** **The study included 69 patients (median age 51, males 93%). Alcohol was the most common etiology; 59% patients belonged to Child-Pugh class B. NSBB was indicated for primary prophylaxis in 36% and secondary prophylaxis in 64% patients. According to the response criteria, 67% patients were found to be acute-hemodynamic-responders. At 6 months, 92% patients were found to be still maintaining their hemodynamic response to carvedilol. Using intention-to-treat analysis, 76% patients maintained their response. These acute responders, on chronic treatment with carvedilol during the 6-month period, had lesser episodes of variceal bleeding, better ascites control, and improved MELD and CTP scores, than non-carvedilol treated non-responders. However, survival remained similar in both the groups.** ***Conclusions:*** **A single-time HVPG measurement with acute-hemodynamic-response-testing is simple and reliable method for identifying patients who are more likely to respond to carvedilol therapy. The HVPG-response is maintained over a long period in majority of these patients and carvedilol therapy leads to better clinical outcome in these patients.** **(J Clin Exp Hepatol 2016;6:175–185)**

Portal Hypertension

Portal hypertension is responsible for most and often lethal complications of cirrhosis such as bleeding from esophagogastric varices, ascites, renal dysfunction, and hepatic encephalopathy. Because of the combined impact of these complications, portal hypertension remains the most important cause of morbidity and mortality in patients with cirrhosis.[1] A decrease in portal pressure is not only protective against the risk of variceal bleeding but is also associated with a lower long-term risk of developing complications and an improved long-term survival. A milestone in therapy was the introduction of non-selective beta-blockers (NSBBs) for the prophylaxis of variceal bleeding. However, in practice, less than 50% of patients are hemodynamic responders to traditional NSBBs such as propranolol or nadolol.[1] Carvedilol is a new NSBB with an additional property of vasodilatation due to its intrinsic anti-α1 adrenergic activity and its capacity to enhance the release of nitric oxide.[2,3] Thus, carvedilol is a more potent agent than other NSBB in reducing portal pressure and is likely to be effective in more patients.

The gold standard method to know whether a patient is a responder to NSBB is to measure the HVPG at baseline, and then repeat HVPG measurement after chronic administration of NSBB. However, concerns have been raised in relation to the feasibility, the clinical appropriateness, the risks, and the costs of repeated HVPG measurement.[4,3] Acute-hemodynamic-response-testing is a technique in which HVPG is repeated at 60–90 min after oral or

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Abbreviations: CTP: Child-Turcotte-Pugh; EVL: endoscopic variceal ligation; FHVP: free hepatic venous pressure; HVPG: hepatic venous pressure gradient; MELD: model for end-stage liver disease; NSBB: non-selective beta-blocker; VBL: variceal band ligation; WHVP: wedged hepatic venous pressure

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intravenous NSBB being tested. Many studies have investigated the role of acute HVPG response to intravenous or oral propranolol in predicting the risk of bleeding and survival.[5–9] We aimed to determine whether a single-time HVPG measurement, using acute-hemodynamic-response-testing, is sufficient to predict long-term response to carvedilol, and whether these responders have better clinical outcome.

PATIENTS AND METHODS

Patients

This was a prospective study conducted in the Department of Gastroenterology at Sir Ganga Ram Hospital, New Delhi, India, between August 2011 and May 2013. The ethics committee of the hospital approved the study and a written informed consent was obtained from all the participants. The study conformed to the Helsinki declaration of 1975 as revised in 1983.

Inclusion Criteria

All consecutive patients of cirrhosis, between ages 18 and 70 years, in whom NSBB was indicated for primary or secondary prophylaxis (i.e. patients with large [>5 mm] esophageal varices[10] or those with varices of any size but with history of variceal bleeding), and who consented to undergo HVPG, were enrolled. The diagnosis of cirrhosis was based on clinical, laboratory, and ultrasonographic data or histology if available.

Exclusion Criteria

(i) Patients already on NSBBs at the time of HVPG; (ii) concomitant HIV infection; (iii) associated severe cardiac or pulmonary co-morbidities; (iv) renal dysfunction (serum creatinine >1.6 mg/dL); (v) grade 3–4 hepatic encephalopathy at the time of enrollment; (vi) hepatocellular carcinoma or other malignancies; (vii) underwent shunt surgery or TIPSS for portal hypertension; (viii) pregnancy; (ix) systolic blood pressure <90 mm Hg at the time of HVPG; and (x) failure to give consent for inclusion in the study.

The baseline clinical and laboratory parameters were recorded in all the included patients.

Aims of the Study

Primary Aim

To determine the proportion of patients who have acute-hemodynamic-response to carvedilol.

Secondary Aims

(i) To assess whether acute-hemodynamic-response is maintained for long-term (6 months); and (ii) to assess whether carvedilol therapy leads to a better clinical outcome in patients who were acute-hemodynamic-responders compared to non-carvedilol treated patients who were not acute-hemodynamic-responders (i.e. acute-hemodynamic-non-responders).

HVPG

HVPG measurement was done after overnight fast, using the standard technique.[11,12] If the patient was on any portal pressure reducing drug, it was stopped prior to HVPG measurement as per following schedule: Beta-blocker was stopped for at least 7 d; terlipressin was stopped for at least 24 h; and somatostatin was stopped for at least 12 h. Under local anesthesia, a 7F vascular sheath (Arrow Medical, Athens, TX, USA) was placed in the right femoral vein or internal jugular vein using the Seldinger technique. HVPG was measured by the standard technique[11,12] in which a balloon catheter was introduced into the middle or right hepatic vein under fluoroscopic guidance. Atmospheric pressure at the level of mid-axillary line was set as the zero reference point. The free hepatic venous pressure (FHVP) was obtained by keeping the catheter free into the lumen of the hepatic vein. The balloon of the catheter was then inflated to wedge the lumen of hepatic vein and pressure recorded. Presence of wedging was confirmed by absence of reflux into the inferior vena cava, after injection of 2 ml intravenous contrast, and appearance of a sinusoidogram. The pressure tracing at this juncture was labeled as wedged hepatic venous pressure (WHVP). HVPG was determined by subtracting free from wedged hepatic venous pressures (WHVP – FHVP). WHVP and FHVP readings were repeated several times (at least thrice) and average value was taken. If the difference between the two HVPG readings was more than 1 mm Hg, all the readings were discarded and fresh set of measurements were taken. The normal accepted value for HVPG is 1–5 mm Hg.

After taking the baseline HVPG reading, the patient was given 25 mg of carvedilol orally, on table. A repeat HVPG measurement was done 1 h after giving carvedilol. The post carvedilol HVPG value was compared with the baseline HVPG value. On the basis of HVPG response to carvedilol, patients were classified as:

- *Acute-hemodynamic-responders*: Fall in HVPG ≥10% from baseline or absolute HVPG value declining to <12 mm Hg.
- *Acute-hemodynamic-non-responders*: Not satisfying above criteria.

Treatment and Follow-Up

All the acute-hemodynamic-responders were started on carvedilol at a dose of 12.5 mg/d (in two divided doses), in addition to the standard endoscopic therapy (endoscopic variceal ligation for esophageal varices and cyanoacrylate glue for gastric varices). Patients who were acute-hemodynamic-non-responders received standard endoscopic therapy alone.

All patients were followed for 6 months and were monitored at regular intervals for complications of cirrhosis (variceal bleeding, ascites, hepatic encephalopathy, etc.)