Research Article

EASL EUROPEAN ASSOCIATION FOR THE STUDY OF THE LIVER | JOURNAL OF HEPATOLOGY



# Carvedilol *vs.* esophageal variceal band ligation in the primary prophylaxis of variceal hemorrhage: A multicentre randomized controlled trial

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**Background & Aims**: Esophageal variceal bleed is a major problem in patients with cirrhosis. Endoscopic variceal ligation (EVL) has been shown to be equal to or better than propranolol in preventing first bleed. Carvedilol is a non-selective β blocker with alpha-1 adrenergic blocker activity. Hemodynamic studies have shown carvedilol to be more effective than propranolol at reducing portal pressure. We compared efficacy of carvedilol with EVL for primary prophylaxis of esophageal variceal bleed.

**Methods**: Cirrhotic patients with esophageal varices were randomized to carvedilol 12.5 mg daily or EVL at three university hospitals of Pakistan. End points were esophageal variceal bleeding, death or liver transplant.

**Results**: Two hundred and nine patients were evaluated. Eighty two and eighty six patients were randomized in carvedilol and EVL arms respectively. Mean age was 48 ± 12.2 years; 122 (72.7%) were males; 89.9% had viral cirrhosis; mean Child-Pugh score was 7.3 ± 1.6 and mean follow up was 13.3 ± 12.1 months (range 1–50 months). Both EVL and carvedilol groups had comparable variceal bleeding rates (8.5% *vs.* 6.9%), bleed related mortality (4.6% *vs.* 4.9%) and overall mortality (12.8% *vs.* 19.5%) respectively. Adverse events in carvedilol group were hypotension (n = 2), requiring cessation of therapy, while transient nausea (n = 18) and dyspnea (n = 30) resolved spontaneously. In the EVL arm, post banding ulcer bleed (n = 1) and chest pain (n = 17), were termed as serious adverse events while transient dysphagia (n = 58) resolved without treatment.

**Conclusions**: Although our study is underpowered, the findings suggest that carvedilol is probably not superior to EVL in preventing first variceal bleed in patients with viral cirrhosis.



Keywords: Portal hypertension; Variceal hemorrhage; Cirrhosis; Randomized controlled trial; Carvedilol; Endoscopic variceal ligation; Primary prophylaxis.
*Received 19 July 2013; received in revised form 19 November 2013; accepted 20 November 2013; available online 28 November 2013*

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*Abbreviations:* EVL, esophageal variceal ligation; EVB, esophageal variceal bleed; HCV, hepatitis C virus; HBV, hepatitis B virus; HDV, hepatitis delta virus; PVT, portal vein thrombosis; HCC, hepatocellular carcinoma; GCP, good clinical practice; ER, emergency room; GV, gastric varix; EV, esophageal varix; EKG, electrocardiogram; BCU, bleeding care unit; Hb, hemoglobin; ITT, intention to treat; CI, confidence interval; IHD, ischemic heart disease; HVPG, hepatic venous pressure gradient; EGD, esophago-gastro-duodenoscopy; TIPS, transjugular intrahepatic portosystemic shunt; PSE, porto-systemic encephalopathy.

## Introduction

Variceal bleed is a dreaded complication of portal hypertension and screening endoscopy for varices is recommended in cirrhotic patients. Varices develop at the rate of 5% per year and one third will bleed [1]. Nonselective β blockers (Propranolol or Nadolol) reduce portal pressure by decreasing cardiac output (β-1 effect) and, more importantly, by producing splanchnic vasoconstriction (β-2 effect), thereby reducing portal blood flow. A decrease in hepatic venous pressure gradient (HVPG) <12 mmHg essentially eliminates the risk of hemorrhage and improves survival [2], while reductions <20% from baseline [3] or even <10% from baseline [4] significantly decrease the risk of first variceal hemorrhage. Endoscopic variceal band ligation (EVL) is another modality of treatment of esophageal varices and meta-analysis showed EVL to be associated with significantly lower incidence of first variceal hemorrhage without differences in mortality compared to β blockers [5]. Although the EVL group has a significantly lower rate of adverse events, the EVL events are more severe and include bleeding from ligation-induced esophageal ulcers [6].

Carvedilol possesses both non-selective β1/2-antagonist and α1-receptor antagonist activity [7]. It has a greater potential for lowering portal pressure than propranolol due to its dual action [8,9]. A fall in both intrahepatic and porto-collateral resistance contributes to the enhanced effects on portal pressure reduction through blockade of alpha-1 receptors as has been shown with prazosin [10]. A reduction in HVPG of 8%–43% has been observed with carvedilol in published hemodynamic studies [10–16]. Carvedilol was also found to have a greater portal hypotensive effect than propranolol in randomized controlled hemodynamic studies [11,12,15].

There is scanty data in the literature comparing carvedilol and EVL in the primary prophylaxis of variceal hemorrhage [17]. Our

study was aimed at comparing the efficacy of carvedilol with EVL for primary prophylaxis of variceal bleed and mortality in patients suffering from post-viral cirrhosis and portal hypertension.

## Patients and methods

### *Study design and settings*

This investigator initiated multicenter randomized controlled trial was conducted in three tertiary care hospitals in Karachi, Pakistan (Section of Gastroenterology, Department of Medicine, Aga Khan University; National Institute of Liver & Gastrointestinal Diseases, Dow University of Health Sciences and Medical ward VII of Jinnah Post Graduate Medical Center). Enrollment of patients into the study was done between May 2007 and September 2011. Approval of the Institutional Review Boards of each of the institution was taken prior to initiation of the trial. Written informed consent from each subject was taken in accordance with the Declaration of Helsinki. The study was conducted following the Good Clinical Practice (GCP) guidelines. An independent data safety monitoring board monitored the trial and had access to data. The study protocol was registered at www.clinicaltrials.gov (*ClinicalTrials.gov identifier:* NCT 01070641).

### *Patient selection*

Patients with cirrhosis without history of variceal bleed, who were booked for screening endoscopy for varices, were the study population. We included male and female patients between 18 and 75 years of age, who had medium or large sized esophageal varices (Grade II–IV) [18]. The diagnosis of cirrhosis was made on the basis of clinical, radiological, biochemical features, and liver histology where available.

We excluded patients who were pregnant or lactating, had allergy to carvedilol or reactive airway disease, already on Beta adrenoceptor blocker treatment, presence of any hepatic or other malignancy, which could impair longevity of life or presence of severe systemic illness, which could impair the subject's ability to participate in the trial, psychiatric or mentally handicapped people that would prevent taking informed consent and refusal to give consent. We also excluded patients who had gastric varices alone.

### *Randomization and study treatment*

Study subjects fulfilling the enrolment criteria after screening endoscopy for varices and having signed the informed consent were randomized to receive either carvedilol or EVL. Randomization was done following screening endoscopy with 1:1 simple randomization, centrally. Each of the three study sites were provided with the serially labeled sealed opaque envelopes containing treatment assignment information. These envelopes were opened in a consecutive manner to receive either carvedilol or EVL depending on the randomization assignment.

Patients who were randomized for EVL underwent the procedure within 48 h of randomization using Saeed Six Shooter Multi-Band Ligator® (Wilson-Cook Medical, North Carolina, USA) attached to a video endoscope (Olympus GIF H-180, Tokyo, Japan). Attending gastroenterologists with at least 5-years' experience performed all EVL procedures. This was subsequently repeated every three weeks until obliteration of varices was achieved. Obliteration of varices was defined as no varices or only small varices (varices which were small and flattened on air insufflations). Subsequent endoscopy sessions were done at intervals of 6 months. If varices recurred on surveillance Esophagogastroduodenoscopy (EGD), the protocol for eradication of varices as described above was repeated.

Patients randomized to carvedilol arm were given carvedilol (Carvida®, manufactured by Ferozsons laboratories, Pakistan) in an initial dose of 6.25 mg once a day, which was increased to 6.25 twice a day after an interval of 1 week. This dose is generally well tolerated in cirrhotics and has been used in other studies [17]. Higher doses are likely to produce symptomatic hypotension and thus impair tolerability. Side effects and adverse reactions for each treatment arm were also recorded.

### *Follow up*

The initial visit after introduction of carvedilol was at 2 weeks, followed by one at 6 weeks and then at 3 monthly intervals in both arms of treatment. Clinical examination was carried out at each visit. Hematological and biochemical parameters were obtained on each visit. Abdominal ultrasound for hepatoma surveillance was done at six months intervals. Compliance to carvedilol was confirmed by interviewing the patient and the family. Blood pressure and peripheral pulse response also guided towards patient compliance with carvedilol.

Patients were considered to have achieved end points on ITT if they bled, died, were lost to follow up, underwent liver transplantation or transjugular intrahepatic portosystemic shunt (TIPS) placement.

### *End points and outcomes*

The primary end point was variceal bleed defined as overt hematemesis and/or melena with endoscopic evidence of variceal bleeding or signs of recent bleed and at least 2 g/dl drop in hemoglobin within 24 h of admission Baveno IV [18]. Bleeding was managed by standard measures using transfusion of blood/blood products, vasoactive drugs (Terlipressin/Octreotide), antibiotics and endoscopic means (EVL or sclerotherapy).

Secondary end-points included overall and bleed related mortality defined as death within 6 weeks of index bleed [18].

### *Statistical analysis*

A total of 77 patients were required in each arm of the trial in order to achieve 80% power at 5% level of significance. We assumed that carvedilol will be more effective than EVL with a bleeding rate of 5% in the carvedilol group and 20% in the EVL group at 24 months. The figure for EVL arm was derived from a published study [19]. Sample size was inflated by 10% for dropout (lost to follow up) or consent withdrawal. No interim analysis was planned or performed. Mean ± Standard Deviation for age, Child's score and laboratory characteristics was used for the two study groups and any differences in the groups were analyzed using an unpaired Student's *t* test. Frequencies (%) for gender, ultrasound characteristics and etiology of cirrhosis were presented. Non-parametric data were analyzed using the Chi square test. Cumulative bleeding and survival were expressed using the Kaplan-Meier method and the differences assessed using the log-rank test. Cox proportional hazard ratio was used to assess variables predicting end points. Intension to analysis was used. Variables with $p < 0.05$ following univariate analysis were entered into multivariate analysis. SPSS (version 19, Chicago, IL) statistical package was used for analysis.

## Results

A total of 209 patients undergoing screening EGD for varices were evaluated and out of them a total of 168 patients were enrolled into the study. Forty one patients were excluded due to refusal to give consent or not meeting enrolment criteria. Following endoscopy, 82 and 86 patients were randomized to receive either carvedilol or EVL respectively. The two arms of the study are elaborated in Fig. 1. The base line characteristics were comparable in the two arms. Although there were more patients randomized to the EVL arm with large esophageal varices compared to carvedilol arm, this difference was not statistically different. Ten patients (12.2% and 11.6% respectively) in each arm of the study had history of Porto-systemic encephalopathy (PSE) stage I of West Haven criteria in the past. However, they had no PSE at the time of enrolment (Table 1).

Etiology of viral cirrhosis was predominantly HCV related. However, 14 (17%) patients in the carvedilol arm and 11 (12.7%) in the EVL arm suffered from HBV related liver disease, either alone or in combination with HCV or HDV infection. Ascites was present in 33 (40.3%) in the carvedilol and 32 (37.6%) patients in the EVL arm (Table 1). This was treated with Spironolactone (50–100 mg)/day with the addition of frusemide as required. On treatment, it was observed only in 5 (6.1%) and 6 (6.9%) patients in the two groups respectively at six months of follow up. There was no significant net weight gain in either group of patients on follow up. Carvedilol arm patients weighed