



Original Article

Carvidelol Vs Propranol for Secondary Prophylaxis of Variceal Hemorrhage in Liver Cirrhosis Patients

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ABSTRACT

Propranolol and Carvedilol are the currently used medications for main prophylaxis of variceal bleeding. **Objective:** To investigate the efficacy of carvedilol vs propranolol for prevention of variceal hemorrhage in liver cirrhosis patients. **Methods:** This prospective comparative study was carried out on 196 cirrhotic patients in the Gastroenterology Department of Lady Reading Hospital, Peshawar in collaboration with Pharmacology department of Khyber Medical University, Peshawar from July 2018 to June 2020. Patients with no prior history of primary variceal prophylaxis treatment and variceal bleeding were enrolled. All the patients were categorized into two groups: Group-I (Carvedilol) and Group-II (propranolol). Frank hematemesis, melena, and endoscopic assessment was used for the evaluation of variceal bleeding. **Results:** Of the total 196 liver cirrhosis patients, Group-I and Group-II had 102 (52%) and 94 (48%) respectively. Ultrasonography found splenomegaly in 88% of cases and moderate to severe ascites in 42.6% of the patients investigated. The success rate of carvedilol and propranolol group was 76% and 64.8% respectively. The side-effects and complication rate were significantly lower in Group-I than Group-II. The prevalence of variceal bleeding was 16.7% (n=17) and 11.7% (n=11) respectively. **Conclusions:** Carvedilol is an excellent treatment alternative for prevention of variceal bleeding than propranolol in terms of side-effects and complications rate.

INTRODUCTION

Gastric varices and bleeding esophageal are major complications of portal hypertension which increase the mortality rate by one-third in liver cirrhosis patients [1]. The mortality rate of variceal bleeding varied from 10% to 20% [2, 3]. The variceal hemorrhage advance treatment has significantly lowered the mortality rate, bleeding recurrence risk, and gastroesophageal varices rupture [4]. For variceal prophylaxis of medium or large varices, band

ligation, carvedilol, and propranolol were advised beta-blockers. Based on knowledge and available resources, contraindications, features, side effects, and preferences of patients should be considered [5]. Carvedilol is a viable option that has recently been studied for decreasing portal hypertension. NSBBs, mainly carvedilol, are used as stand-alone medicinal treatment in primary prophylaxis to avoid variceal hemorrhage and the formation of ascites [6, 7].

The conventional preventative treatment for individuals who have previously bled is a mix of medicinal and endoscopic therapy [8]. Moreover, earlier research has recognized NSBBs as the secondary prophylaxis cornerstone since their endoscopic band ligation (EBL) significantly improves outcomes [9, 10]. The risk of re-bleeding and mortality is notably low when patients' HVPG drops by 20% or to an absolute value of 12 mm Hg (HVPG response) [11]. Previous studies have evaluated the hemodynamics response of carvedilol: In a brief pilot trial of 16 patients, HVPG fell from 16.7 to 13.6 mm Hg without a substantial drop in azygos blood flow [12]. Mean artery pressure (MAP) fell from 94.8 to 84 mm Hg, however only in individuals with ascites did heart rate fall. The present study aimed to assess the efficacy of carvedilol vs propranolol for secondary prophylaxis of variceal hemorrhage in liver cirrhosis patients.

METHODS

This prospective comparative study was carried out on 196 cirrhotic patients in the Gastroenterology Department of Lady Reading Hospital, Peshawar in collaboration with Pharmacology Department of Khyber Medical University, Peshawar from July 2018 to June 2020. Patients with no prior history of primary variceal prophylaxis treatment and variceal bleeding were enrolled. In order to detect the difference in responder's proportion 0.32 by assuming the propranolol and carvedilol group response rate 37% and 63% respectively taken average of previously reported response, 80% statistical power, and 5% level of significance. Considering a 25% drop-out patients' rate, 100 patients should be allocated for each group. However, we had challenges in recruiting the study subject, and 196 patients were finally considered. Patients who refused to participate, suffering from liver cirrhosis, chronic kidney disease, neoplastic disease, and showed contraindication to beta blockers such as uncontrolled diabetes, asthma, heart failure, obstructive pulmonary disease, arteria hypotension with SBP <90 mm Hg, atrioventricular block, and bradycardia with HR ≤40 bpm were excluded. The diagnostic criteria for liver cirrhosis patients included clinical signs such as splenomegaly, ascites, and collateral venous presence, endoscopic signs i.e., esophageal varices, ultrasound signs such as enlarged portal vein >15 mm, periportal fibrosis, splenomegaly, and portosystemic collaterals. All the patients were categorized into two groups: Group-I (Carvedilol) and Group-II (propranolol). Frank hematemesis, melena, and endoscopic assessment was used for the evaluation of variceal bleeding. All the patients underwent full history-taking, prior hematemesis and melena attack's history, clinical examination, ischemic heart disease, asthmatic attacks, liver cell failure, and

hypertension. Viral marker, CBC, blood glucose, renal function tests, and profile of liver biochemical were tested. Liver size, liver cirrhosis existence, splenomegaly, portal vein thrombosis, ascites, and hepatocellular cancer was confirmed through abdominal ultrasonography. SPSS version 27.0 was used to collect and statistically evaluate data.

RESULTS

Of the total 196 liver cirrhosis patients, Group-I and Group-II had 102 (52%) and 94 (48%) respectively. Out of total, there were 60 (30.6%) male and 136 (69.4%) female. The overall mean age of patients in group-I and group-II was 50.6 ± 6.4 years and 50.2 ± 10.6 years respectively. The most prevalent cause of cirrhosis and portal hypertension was HCV found in 68% cases in Group-I as compared to 74% in Group-II. Ultrasonography found splenomegaly in 88% of cases and moderate to severe ascites in 42.6% of the patients investigated. The success rate of carvedilol and propranolol group was 76% and 64.8% respectively. The mean dosage of carvedilol and propranolol group patients was 12.48 ± 6.28 mg/day and 42.82 ± 7.28 mg/day. The side-effects and complication rate were considerably lower in Group-I than Group-II. The prevalence of variceal bleeding was 16.7% (n=17) and 11.7% (n=11) respectively. There was no statistically significant difference between patient groups I and II. Table-I represents the comparison of baseline characteristics of group-I and group-II patients.

Table 1: Baseline characteristics of patients

Parameters	Group-I (Carvedilol) N=102	Group-II (Propranolol) N=94
Age (years)	50.6 ± 6.4	50.2 ± 10.6
Gender N (%)		
Male	36 (35.3)	24 (25.5)
Female	66 (64.7)	70 (74.5)
Chronic HCV (%)	68	74
Chronic HBV	18	16
ALT (IU/L)	56.38 ± 36.68	42.62 ± 31.86
AST (IU/L)	54.52 ± 34.63	48.84 ± 32.82
T. bilirubin (mg/dl)	3.12 ± 2.42	2.68 ± 1.86
Creatinine (mg/dl)	2.58 ± 0.49	2.58 ± 0.64
Hemoglobin (g/dl)	107.72 ± 45.84	97.82 ± 54.38

Abdominal ultrasonography findings in both groups are shown in Table 2.

Table 2: Abdominal ultrasonography findings in both groups

Abdominal ultrasonography findings	Group-I (Carvedilol) N=102	Group-II (Propranolol) N=94
Shrunken liver (%)	26	28
Splenomegaly (%)	88	94
Moderate/marked ascites (%)	24	32

Endoscopic findings and pathological grading of patients compared in both groups are shown in Table 3.

Table 3: Endoscopic findings and pathological grading of patients compared in both groups

Endoscopic findings	Group-I (Carvedilol) N=102	Group-II (Propranolol) N=94
Medium/large varices (%)	66/34	62/38
Portal hypertensive gastropathy mild/severe (%)	42/58	64/36
Pathological grading Mild/moderate/severe (%)	42/22/36	44/32/24

Comparison of side effects, success rate, and child score in both groups are represented in Table 4.

Table 4: Comparison of side effects, success rate, and child score in both groups

Parameters	Group-I (Carvedilol) N=102	Group-II (Propranolol) N=94
Side effects	16.4%	36.8%
Success rate	76%	64.8%
Child score	12/36/52	10/24/66

DISCUSSION

The present study mainly investigated the efficacy of carvedilol vs propranolol for secondary prophylaxis of variceal hemorrhage in cirrhotic patients and found that carvedilol is a better therapeutic option than propranolol for preventing variceal bleeding. Carvedilol generates greater decreases in HVPg than propranolol in secondary prophylaxis of variceal bleeding, which is associated with a lower risk of re-bleeding, extra nonbleeding decompensation, and liver-related death. Carvedilol group had lower complication rate and side effects than propranolol group. The current study suggested therapy choices among the several proposed treatments. Additionally, the current investigation compared and validated the effectiveness, side effects, and outcomes of carvedilol and propranolol for prevention of variceal bleeding. Meta-analyses by Sersté *et al.*, eliminated the greater success rate of carvedilol because this marginal benefit is impacted by technical considerations, since carvedilol is operator dependent; endoscopist expertise combined with good technique impacts the outcomes [13, 14]. Regarding other aspect of non-selective β -blockers such as propranolol might show uncertainty in causing the hepatorenal syndrome or acute kidney injury by reducing patient's survival rate in liver cirrhosis decompensation [15]. Carvedilol has more strong hemodynamic effects than propranolol, as well as a larger risk for causing systemic hypotension and potentially circulatory malfunction [16]. However, in order to attain the desired HR, a greater dosage of carvedilol (25 mg/day) was required. Notably, continuous treatment of low-dose carvedilol may contribute to a

significant decrease in HVPg without causing severe systemic hypotension. Carvedilol has a favorable response in patients with ascites and has no significant adverse effects. Our findings further suggest that 6 weeks of low-dose carvedilol is not only similar to propranolol, but substantially more successful in lowering portal pressure in patients with decompensated liver cirrhosis, despite the fact that none of our patients had a CP score of 12 or refractory ascites [17]. The propranolol group had a higher risk of extra medication-related issues, which lowered compliance and drug intake when compared to other lines of treatment. The recurrence rate of varices after band ligation removal was 13.6% after a year of follow-up. Its recurrence rate is comparable to that of Kim *et al.*, [18]. In our experiment, carvedilol had a better success rate than propranolol, with fewer side effects that did not need drug withdrawal. Prior research has demonstrated that carvedilol is an effective medicine for the primary prevention of variceal bleeding, with a favorable prognosis and few side effects [19]. The liver cell failure and severity, as measured by the Child score, was assessed throughout a one-year period in order to determine the variceal prophylaxis primary effect. Although advanced Child scores have previously been linked to failure to control variceal bleeding and re-bleeding [20, 21], Child C patients were not linked to treatment failure. Propranolol and carvedilol dramatically improved portal hypertensive gastropathy [22, 23]. In contrast to beta-blockers, which do not lower portal pressure [24]. Hence, the severity of side effects, the experience of the treating physician, as well as patient and compliance, influence the choice of treatment strategy for primary variceal hemorrhage prevention. Further research using carvedilol for primary prevention of variceal bleeding is encouraged, with results compared to combination therapy with band and propranolol or each preventative approach alone.

CONCLUSIONS

Carvedilol is an excellent treatment alternative for prevention of variceal bleeding than propranolol in terms of side-effects and complications rate. In secondary prophylaxis of variceal bleeding, carvedilol induces superior reductions in HVPg than propranolol, and so is related to decreased incidence of re-bleeding, additional nonbleeding decompensation, and liver-related mortality.

Authors Contribution

Conceptualization: K, MSK

Methodology: MS, SN

Formal analysis: ZI

Writing-review and editing: MSK, MF, IU, SRG

All authors have read and agreed to the published version of the manuscript.

Conflicts of Interest

The authors declare no conflict of interest.

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