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Original Research Paper

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RANDOMIZED CONTROLLED STUDY OF CARVEDILOL VS CARVEDILOL PLUS VARICEAL LIGATION FOR THE PRIMARY PROPHYLAXIS OF ESOPHAGEAL VARICEAL BLEED.

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ABSTRACT **Background and Aim:** Modalities available for primary prophylaxis of variceal bleed are non-selective beta-blockers(NSBB), carvedilol and local therapy. The efficacy of combination of NSBB and Endoscopic Variceal Ligation (EVL) was investigated in the past and showed contrasting results. However, there have been no clinical studies assessing the efficacy of carvedilol versus combination of carvedilol plus EVL for primary prophylaxis of variceal bleed. The aim of this study was to compare carvedilol and combination of carvedilol plus EVL for the primary prophylaxis of esophageal variceal bleed. **Methods:** In this randomized controlled study, 113 chronic liver disease (CLD) patients with small esophageal varices with red color signs (RCS) and large varices with or without RCS, with no previous bleeding were randomized to either carvedilol or carvedilol plus EVL therapy. Analysis was done at 6 months after enrolment. **Results:** Fifty-seven patients were randomized to carvedilol and fifty-six to carvedilol plus EVL. Baseline characteristics did not differ between the groups. Among subjects received carvedilol 14%(n=8) had variceal bleeding, whereas 10.7%(n=6)) had bleeding in carvedilol plus EVL group. However, the difference was not statistically significant(p=0.592). In carvedilol group, 3.5%(n=2) died during the study period, where as in another group 8.9%(n=5) died (p=0.232). Child (B than A) and MELD-Na(>15) score were found to significantly associated with variceal bleeding across the groups. **Conclusion:** Carvedilol alone is as effective as combination of carvedilol plus EVL for prevention of first bleed in patients with CLD.

KEYWORDS : Portal hypertension; Variceal hemorrhage; Carvedilol mono therapy; Endoscopic variceal ligation.

INTRODUCTION

Cirrhosis is a major chronic health problem worldwide. Portal hypertension is an almost unavoidable complication of cirrhosis, which can lead to various complications. Variceal bleeding, the most serious complication of portal hypertension, is a medical emergency associated with 15–25% mortality at 6 weeks, in spite of recent progresses in the management strategies.[1] Primary prophylaxis is universally recommended for cirrhotic patients at high risk of first variceal bleeding. Therapeutic options currently available are novel non selective beta blockers (NSBBs - Propranolol, nadolol), carvedilol (non-cardio-selective beta blocker + alfa-1 blocker) and local therapy i.e. EVL (Endoscopic Variceal Ligation).[2]

A recent network meta-analysis comparing the efficacy of different approaches in primary prevention of esophageal variceal bleeding included 32 randomized clinical trials.[3] The study results found that carvedilol monotherapy, EVL monotherapy, and EVL in combination with NSBB were associated with decreased episode of first variceal bleeding when compared to placebo, and carvedilol was ranked highest for primary prevention of variceal bleeding. However, there was no mortality benefit with carvedilol, and combination therapy (NSBB/EVL) was ranked highest mortality benefit.[3] This is possibly attributed to the paucity of randomized controlled trials including carvedilol. Moreover, a large retrospective study demonstrated a 41% reduction in mortality risk with carvedilol therapy recently.[4] Therefore, there is a need for further trails using carvedilol to elucidate the potential benefits of this drug in terms of mortality benefit.

To date, there are no published clinical trail using combination therapy of carvedilol plus EVL in the primary prophylaxis of variceal bleeding. Considering the absence of mortality benefit with carvedilol, recent studies recommend the NSBB as the preferred initial approach for primary prophylaxis of esophageal variceal bleeding.[3] However, there are no published studies evaluating mortality benefit of combination therapy with carvedilol plus EVL.

The aim of this randomized controlled study is to compare carvedilol versus carvedilol plus EVL in the primary prophylaxis of oesophageal variceal bleed and to compare any mortality benefit of combination therapy over carvedilol mono therapy.

MATERIALS AND METHODS:

Study design: This was a randomized controlled trial conducted in a tertiary care centre in south Kerala, India, over a period of 18 months from January 2017 to June 2019. The trial was undertaken with the approval of the local research ethics committee, written informed consent of each subject, and in accordance with the Declaration of Helsinki (1989) of the World Medical Association.

Patients:

Patients eligible for the trial were selected from consecutive patients attended our department form September 2017 to February 2019. The entry criteria was cases with cirrhosis with small esophageal varices with red color signs (RCS) and large varices with or without RCS, with no previous bleeding were included. Cirrhosis was diagnosed on the basis of clinical, radiological and laboratory tests. Exclusion criteria were as follows: age < 18 years, allergy to carvedilol, presence of ascites/ hepatorenal syndrome, previous exposure to beta-blockers or nitrates, presence of malignancy, presence of severe systemic illness (cardiorespiratory, active sepsis), known cases of bronchial asthma or chronic obstructive pulmonary disease, psychiatric disease or learning difficulty, systolic blood pressure < 90 mmhg & pulse rate <50 beats / min, patients not willing to give consent, and pregnant woman.

Data Collection:

After recording demographic data (age, gender), we took

detailed history of liver disease, bleeding manifestations, medication details and other co-morbidities. Vital examination and general survey were conducted to detect stigmata of chronic liver disease and other system findings. Liver function tests, renal function tests, sodium, potassium, coagulopathy and hematology (complete blood count) parameters were done. Ultrasonography abdomen was done as a part of diagnosis of cirrhosis. Upper GI endoscopy was done in all subjects and by using AASLD (American association for Study of Liver Diseases) classification we classified esophageal varices as: small < 5 mm and large > 5 mm. Subjects qualified inclusion criteria were enrolled in study.[5]

We randomized all eligible patients into two groups (1:1 ratio) by simple randomization technique (Computer based numbers) and subjects were intervened with carvedilol in one group and carvedilol plus EVL in other group.

Treatments:

In the combination therapy arm, the banding was performed using Multi-shot EVL device by senior fully trained endoscopists or under their direct supervision. Varices were banded starting at the gastroesophageal junction and approximately 5 cm proximally. Following randomization, patients underwent EVL every 2-8 weeks until eradication.

Carvedilol was administered orally at an initial dose of 6.25 mg per day. The dose was further increased to a target dose of 12.5 mg per day if systolic blood pressure did not fall below 90 mm Hg. Side effects or adverse reactions for both treatment arms were also recorded.

Follow-up:

The initial clinic visit was 1 week after introduction of carvedilol and then once in two weeks for one month then at monthly intervals. Full biochemical and hematological profile was obtained at each consultation. Clinical examination was also performed. Compliance to carvedilol was assessed through direct questioning and collateral history from relatives. Follow-up was continued in both treatment arms for 6 months. Analysis was done after 6 months of enrollment (figure 1).

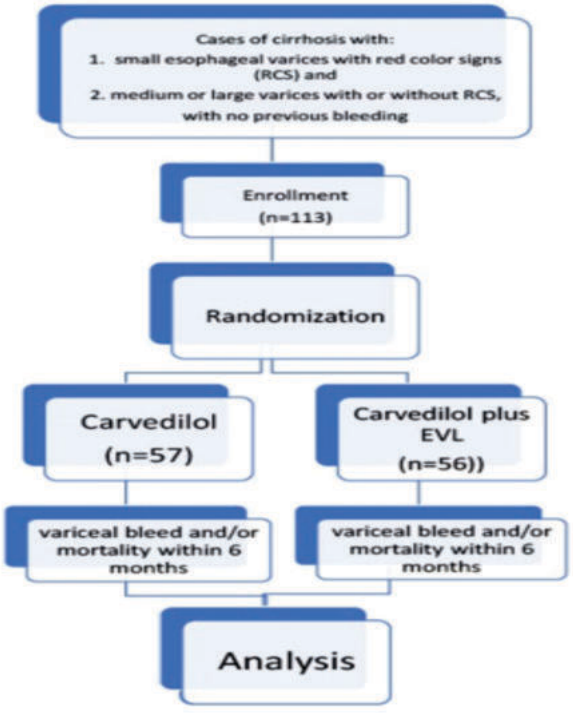

Figure 1: Algorithm of the study.

Definitions of End Points and Outcomes:

The primary end point was the first variceal bleed, defined as hematemesis and/or melena with endoscopic evidence of variceal bleeding. The definition also included bleeding from banding ulceration. Secondary end points included overall mortality, and bleeding-related mortality defined as death within 6 weeks of the index variceal bleed. Other outcomes assessed included side effects resulting in treatment discontinuation.

Statistical Analysis:

All data was entered into Microsoft Excel and analysed using the statistical software Statistical Product and Service Solutions (SPSS) version 16.0. Descriptive statistics were summarized using means with Standard Deviations (SDs). Chi-square test was used for the comparison of categorical variables. Risk factors for variceal bleeding and mortality were assessed using Logistic Regression. A p-value less than 0.05 was considered statistically significant.

RESULTS:

A total of 113 patients were randomized for entry into the trial, 57 in the carvedilol arm and 56 in the carvedilol plus EVL arm. The baseline characteristics of the participants were well-matched across the groups (table 1).

Table 1: Distribution of gender and age in both study groups.

Gender	Carvedilol (n=57)		Carvedilol + EVL(n=56)		Total(n=113)		P value
	N	%	N	%	N	%	
Male	45	78.9	45	80.4	90	79.6	0.85
Female	12	21.1	11	19.6	23	20.4	
Age							
<45yrs	2	3.5	12	21.4	14	12.4	0.004*
>45yrs	55	96.5	44	78.6	99	87.6	

Alcoholic liver disease followed by NAFLD (Non-Alcoholic Fatty Liver Disease) was found as most common cause of liver disease in both groups.

Outcomes:

Variceal Bleeding: Variceal bleeding occurred in eight patients (14%) in the carvedilol arm and 6 patients (10.7%) in the carvedilol plus EVL arm during the follow-up period. However, the difference was not statistically significant (p=0.6). In univariate analysis, Child (B than A) and MELD-Na (>15) score were found to be significantly associated with variceal bleeding (table 2).

Table 2: Univariate analysis of factors affecting variceal haemorrhage.

Variable	Exp (β)	95% CI	P value
Gender			
Female(ref)			
Male	0.269	0.033-2.173	0.22
Age			
<45yrs(ref)			
>45yrs	0.509	0.061-4.22	0.53
Etiology			
ALD	-	-	-
NAFLD	-	-	-
Viral	-	-	-
Others	-	-	-
Varix type			
Small (ref)			
Large	1.250	0.359-4.351	0.73
CHILD Stage			
A(ref)			
B	0.249	0.073-0.085	0.03*
MELD-Na Score			

<15(ref)			
>15	0.139	0.030-0.653	0.01*

*statistically significant at 5% significance level

Mortality:

Seven participants died due to various causes during the study period. Death occurred in two patients (3.5%) in the carvedilol arm and 5 patients (8.9%) in the carvedilol plus EVL arm during the follow-up period. However, the difference was not statistically significant (p=0.23). In the carvedilol arm, one patient died due to variceal bleed and the other due to acute on chronic liver failure. In the carvedilol plus EVL arm, two patients died due to variceal bleeding and the other three died due to post variceal ligation ulcer bleed, sepsis, and acute coronary syndrome, respectively. In univariate analysis, none of the studied factor (age, sex, etiology, varix type, child or meld score) was found to be significantly associated with the risk of mortality (table 3).

Table 3: Univariate analysis of factors affecting mortality.

Variable	Exp (β)	95% CI	P value
Etiology			
ALD(ref)			
NAFLD	2.031	0.374-11.046	0.41
Viral	-	-	-
Others	-	-	-
Varix type			
Small (ref)			
Large	2.430	0.509-11.595	0.26
CHILD Stage			
A(ref)			
B	1.917	0.356-10.327	0.45
MELD-Na Score			
<15(ref)			
>15	0.155	0.018-1.328	0.09

DISCUSSION

This study is the first randomized controlled trial to compare the role of Carvedilol Versus Carvedilol plus Variceal band ligation for the primary prophylaxis of esophageal variceal bleed in patients with high-risk varices and to compare any mortality benefit of combination therapy over carvedilol mono therapy. We have found no statistically significant difference between Carvedilol Versus Carvedilol plus Variceal band ligation in bleeding rate and survival.

Dwinata et al., conducted a systematic review recently regarding Carvedilol *vs* endoscopic variceal ligation for primary prevention of variceal bleeding, and found no statistically significant difference on the events of variceal bleeding (RR: 0.74, 95%CI: 0.37-1.49), all-cause mortality (RR: 1.10, 95%CI: 0.76-1.58), and bleeding-related mortality (RR: 1.02, 95%CI: 0.34-3.10) in patients who were treated with carvedilol compared to EVL.[6] A multi centric randomised study from South Asian region involving 204 patients also found no significant difference in efficacy between carvedilol and EVL in preventing variceal bleeding.[7] However, another randomized controlled multicentre trial study by Tripathi et al, who compared carvedilol and EVL for the prevention of the first variceal bleed in 152 cirrhotic patients found that carvedilol had lower rates of the first variceal bleed than EVL (10% versus 23%; P 0.04).[8]

This study also found that 2 patients (3.5%) from the carvedilol mono therapy arm, and 5 patients (8.9%) from the Carvedilol plus EVL arm died during the study period. However, there was no statistically significant difference in mortality between two groups. Previous studies also showed that there was no significant difference in mortality when patients were offered with either carvedilol or EVL.[5] In our study we found that even after combining both carvedilol and EVL, there was no significant benefit in mortality. The most worrisome complication of EVL is post banding ulcer related bleed.[9] However, in our study only one patient had post EVL ulcer with bleed within one month after last EVL episode and succumbed to death. Only few patients had transient dysphagia and retrosternal discomfort during post banding period, but they tolerated well.

The current recommendation for the prevention of variceal rebleeding in cirrhosis patients is to use a combination of EVL and NSBBs (*i.e.*, propranolol or nadolol) or carvedilol. Moreover, carvedilol was proven better than NSBB in reducing hepatic venous pressure gradient (HVPG) in various studies.[10,11] This study revealed no superiority for carvedilol plus EVL over carvedilol in the primary prophylaxis of esophageal variceal bleed or any mortality benefit. This current study finding may be of use to physicians working in rural areas or hospitals where an EVL intervention is unlikely.

The present study had the following limitations. It was a single centre study with a small sample size which limit generalisation of our study results at population level. Moreover, the diagnosis and assessments were both carried out by the same person, and no proper blinding was done in the study. Followup was done only for a relatively short period (6 months). Furthermore, HVPG measurement was not done, hence accurate improvement in portal hypertension cannot be addressed.

In conclusion, we have shown that carvedilol alone is as effective as combination of carvedilol plus EVL in preventing first bleed in patients with chronic liver disease with portal hypertension. Moreover, there was no significant difference in 6-month mortality between use of carvedilol alone and combined carvedilol plus EVL. Further multi centric studies should be done in larger sample size and for longer duration to strengthen our study findings.

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