



ORIGINAL ARTICLE

## Efficacy of propranolol versus carvedilol in prophylaxis of variceal bleeding: Randomized clinical trial.

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**ABSTRACT... Objective:** To compare the efficacy of carvedilol and propranolol for prophylaxis of variceal bleeding in cirrhotic patients. **Study Design:** Randomized Controlled Trial. **Setting:** Department of Gastroenterology and Hepatology, PIMS, Islamabad. **Period:** 1st January 2022 to 31<sup>st</sup> of December 2022. **Material & Methods:** A total of 260 patients reporting at the department suffering from liver cirrhosis with medium or large esophageal varices and had never reported for variceal bleeding previously. The patients were randomized in to 2 equal groups of 130 each through computer generated randomization. Patients in Group-A were started on dose of carvedilol 6.25mg once daily initially for 1 week, subsequently titrated to twice daily 6.25mg and titrated up if needed to maximum of 25mg twice daily. Patients in Group-B received a dosage of propranolol 20 mg BID which then escalated weekly in 20 mg steps if needed and doses were adjusted as per targeted heart rate and systolic BP. Patients were followed up over 1 year for any event of variceal bleeding. **Results:** Mean overall age in this study was 42.13±10 years. The ratio of male patients was higher than female patients (60% VS 40%). Carvedilol prevented variceal bleeding in 86.15% of the patients while propranolol was effective in preventing variceal bleeding in 75.38% of the patients. Hence carvedilol was significantly more effective than propranolol in preventing variceal bleeding (p=0.02). **Conclusion:** Carvedilol is significantly more effective in prophylaxis of variceal bleeding than propranolol in patients with medium or large esophageal varices.

**Key words:** Carvedilol, Cirrhotic Patients, Primary Prophylaxis, Propranolol, Variceal Bleeding.

### INTRODUCTION

Liver disease is among the leading causes of mortality around the globe and is ranked 5<sup>th</sup> in this list making it as major public health concern.<sup>1,2</sup> Another matter of concern is that the incidence is reported to be on rise and the average age of patients with liver disease is lesser than the patients suffering from cardiovascular and lungs diseases.<sup>1</sup> Portal hypertension and the development of esophageal varices are the serious complications of liver disease and reported to be at an alarming yearly rate of 5%.<sup>3</sup> Esophageal variceal bleeding (EVB) is considered one of the serious complications of portal hypertension in cirrhosis, with high mortality. About 10% to 30% of varices bleed each year.<sup>4</sup> As per another data, the prevalence of esophageal varices is 70% among the patients of cirrhosis and incidence of

variceal bleed in these patients is 30% within a year of developing the disease.<sup>5</sup>

With the progression of liver cirrhosis, the arterial BP tends to reduce and there are deranged hemodynamics recorded at the regional and systemic levels. Systemic hypertension is in fact increased in cirrhotic patients but appears with a declining trend with the progression of the disease. The decreasing trend is explained by the imbalance in the distribution of increased blood volume by the changes in neurohormonal actions and sodium/ water handling.<sup>6</sup> The two commonly recommended strategies for cirrhotic patients utilized to prevent variceal bleeding are endoscopic prophylaxis using variceal band ligation and pharmacologic prophylaxis by recommending non-selective beta-blockers

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(NSBB). Priority is given to  $\beta$  blockers as they are non-invasive, easy to utilize and economical in comparison to band ligation. The priority is also given to the use of beta blockers as there are fatal events reported with band ligation which may be due to bleeding induced from ulcers during the procedure. Despite of some adverse events reported with beta blockers including symptomatic hypotension and dyspnea, there are no reports of fatal events relating to this treatment strategy.<sup>7,8</sup> On the other hand prolonged stay at hospital lead to increased the cost of treatment.<sup>9-13</sup>

Among these NSBB propranolol and nadolol have been recommended for prophylaxis since past 30 years. Propranolol is the most widely used non-selective beta blocker. In the studies conducted with propranolol, a 30% reduction in the variceal bleeding was observed compared to placebo.<sup>14</sup> Carvedilol is used during last decade for prophylaxis purpose in a number of studies.<sup>15,16</sup> An international trial done in 2009 proved only 10% variceal bleed happened with carvedilol compared to 23% with band ligation.<sup>17</sup> An interesting data reveals that in primary prophylaxis, carvedilol provides improved survival rate even when rebleeding was comparable with band ligation.<sup>18,19</sup> As the data regarding superior efficacy of carvedilol in prophylaxis of variceal bleeding is evolving in different study populations, this study was planned to evaluate the efficacy of carvedilol over the other commonly used NSBB propranolol in our population over a follow up of 1 year. This comparison will provide useful data in deciding drug of choice for cirrhotic patients in prophylaxis of variceal bleeding.

## MATERIAL & METHODS

### Study Design and Duration

This randomized controlled (RCT) study was conducted at department of gastroenterology and hepatology, Pakistan Institute of Medical Sciences, Islamabad from 1st of January 2022 to 31st of December 2022 over a period of 1 year after approval from ethics review board (1-1/205/ERB/SZABMU). RCT study design is one of the good designs to conduct clinical studies.<sup>20</sup>

### Sampling Method

Consecutive sampling method was used and the patients were randomized in to 2 equal groups of 130 each through computer generated randomization.

### Study Procedures

A total of 260 patients, between the age of 18 to 60 years reporting at the department, suffering from liver cirrhosis with medium or large esophageal varices and had never reported with variceal bleeding previously (proven through endoscopy) were included in the study through consecutive sampling. The patients were randomized in to 2 equal groups of 130 each through computer generated randomization sheet. Patients in Group-A were started on dose of carvedilol 6.25mg once daily initially for 1 week, subsequently titrated to twice daily 6.25mg and titrated if needed up to maximum of 25mg twice daily. Patients in Group-B received a dosage of propranolol 20 mg BID which will then be escalated weekly in 20 mg steps if needed. The doses were adjusted in both groups to achieve a reduction in heart rate by 25% from the baseline but not below 55 beats/minute or the systolic BP not below 90 mm/Hg. Patients were followed up over 1 year for any event of variceal bleeding. The primary outcome was set as no variceal bleeding during the study period (melena or hematemesis and drop in hemoglobin levels).

### Inclusion and Exclusion Criteria

All those who didn't met the inclusion criteria were excluded and set as high-grade varices, previous history of variceal bleeding, patients already taking any  $\beta$ -blocker or nitrate and malignancy.

### Data Analysis

Collected data analysis were performed while using SPSS version 25. Standard deviation and mean of quantitative variables were calculated for the analysis. Qualitative variables were presented in form of frequency and percentages. Chi-square test was applied to compare efficacy of treatments in both groups while  $p \leq 0.05$  was taken as significant.

**Consent**

The study purpose was explained and consent was taken from the participants on written forms.

**Ethical Approval**

Ethical approval of conducting the study was taken from the ethical committee of the hospital.

**RESULTS**

The majority of the participants were male (group A n=81, 62.30%, group B n=75, 57.6%) and having more than 12 months disease duration. Different demographic characteristics are given in the Table-I in detail.

Demographic Variables		Group-A n=130 n (%age)	Group-B n=130 n (%age)	Total n=260 n (%age)
Gender	Male	81 (62.30)	75 (57.69)	156 (60)
	Female	49 (37.69)	55 (42.30)	104 (40)
Duration of disease	< 12 months	104 (80)	101 (77.69)	205 (78.84)
	> 12 months	26 (20)	29 (22.30)	55 (21.15)
Endoscopic Findings	Medium Varices	73 (56.15)	78 (60)	151 (58.07)
	Large Varices	57 (43.84)	52 (40)	109 (41.92)
Child Pugh Class	A	21 (16.15)	19 (14.61)	40 (15.38)
	B	42 (32.30)	46 (35.38)	88 (33.84)
	C	67 (51.53)	65 (50)	132 (50.76)

**Table-I. Frequency and percentage of demographic variables of patients.**

Age range in this study was from 24 to 60 years with mean age of 42.13±10 years, details of mean age in Group-A and Group-B are shown in Table-II.

Demographics	Group-A Mean±SD (n=130)	Group-B Mean±SD (n=130)
Age (years)	41.80±10.04	42.46±10.03

**Table-II. Patients distribution according to age in both groups.**

Other variables including gender, duration of disease, endoscopic finding and child Pugh class are shown in Table-II with group wise details. Treatment in Group-A was significantly more effective (86.15%) than treatment in Group-B (75.38%) in preventing variceal bleeding in patients with liver cirrhosis at completion of 1 year study period as shown in Table-III.

Efficacy	Group-A n=130	Group-B n=130	P-Value
Yes	112 (86.15%)	98 (75.38%)	0.027
No	18 (13.84%)	32 (24.61%)	
Total	130 (100%)	130 (100%)	

**Table-III. Comparison of efficacy in both groups after 1 year.**

The side effect profile was also calculated for both the groups which shows a statistically significant

higher incidence of reported side effects in Group-B compared to Group-A as shown in Table-IV.

Side Effects	Group-A n=130 n(%age)	Group-B n=130 n(%age)	P-Value
Hypotension, Bradycardia, Asthma	12 (9.23)	36 (27.69)	0.000

**Table-IV. Comparison of reported side effects in both groups.**

**DISCUSSION**

In liver cirrhosis, esophageal variceal bleeding is the most concerning complication, primary prevention is therefore important to reduce the chances of bleeding and its fatal outcomes. NSBB being non-invasive, easy to utilize and affordable have been the topic of research in this indication. The most widely used β blocker for variceal bleeding was propranolol before the use of carvedilol came under discussion. Most of the available comparative data in the primary prophylaxis of variceal bleeding in liver cirrhosis is between band ligation and β blockers and relatively less work is available in comparing the effects of two commonly used NSBB Carvedilol and propranolol. A study published in 2022 by Kanwal N et al., conducted in Pakistani population, compared efficacy of carvedilol and band ligation

in primary prophylaxis of variceal bleed. The efficacy of carvedilol in reducing variceal bleeding was 72.4% over a period of 3 months with a good patient's compliance.<sup>21</sup>

A primary prophylaxis study recently published by Soliman S. in 2023 evaluated the efficacy of carvedilol versus band ligation in hypertensive cirrhotic patients for variceal bleeding. The results reported only 2.6% cases of bleeding (97.4% efficacy) with carvedilol in a study follow up period of 1 year with only 10.46% cases of adverse events. The authors concluded carvedilol as safe and effective in this indication.<sup>22</sup> Khan AM in a study conducted for the purpose of primary prevention of variceal bleeding in Pakistani cirrhotic patients compared the efficacy of carvedilol and propranolol. The results showed a statistically significant success rate of 85.2% with carvedilol compared to 72.7% with propranolol.<sup>23</sup>

Abd El Rahim et al. compared the efficacy of band ligation, propranolol and a rising NSBB carvedilol for primary prophylaxis of variceal bleeding over 1 year period. The results among  $\beta$  blockers showed a 70.2% decrease in variceal bleeding with carvedilol while 65.2% with propranolol. The difference was statistically non-significant. Moreover only 14.2% patients in carvedilol group reported side effects compared to 34.7% in propranolol group.<sup>24</sup> Hence, carvedilol was said to be good alternative medicine to propranolol due to lesser reported side effects.<sup>24</sup> The results of our study are also in line with studies discussed above. The overall mean age of the study population was  $42.13 \pm 10$  years. The percentage of male gender was higher (60%) compared to females (40%). The reported studies results also shown that carvedilol was better tolerated with significantly lesser treatment related side effects including hypotension, bradycardia and asthma.<sup>25</sup>

The results of this study will provide help in deciding the drug of choice for prophylaxis of variceal bleeding in liver cirrhosis patients. The major limitations were however the small sample size and study follow up duration. Future studies will a larger sample size and longer patients follow will be therefore needed for future guidelines.

## CONCLUSION

Among the non-selective  $\beta$  blockers, carvedilol is significantly more effective with lesser side effects and better compliance in prophylaxis of variceal bleeding than the traditionally used propranolol in patients with medium or large esophageal varices.






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### AUTHORSHIP AND CONTRIBUTION DECLARATION

No.	Author(s) Full Name	Contribution to the paper	Author(s) Signature
1	Imran Zeb	Conceptualize and initial draft.	
2	Fazal Rabbi	Data collection and method.	
3	Muhammad Ali	Data entry and management.	
4	Abdul Khalid	Result part and provide support in the manuscript.	
5	Sheheryar Khan	Data analysis.	
6	Sana Mukhtiar Khan	Review and editing the final manuscript.	