doi.org/10.36721/PJPS.2023.36.3.REG.857-862.1

Comparison of carvedilol and propranolol for primary prophylaxis of esophageal variceal bleed in cirrhotic patients

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Abstract: Cirrhosis continues to claim the lives of people worldwide every year. Esophageal variceal bleeding due to portal hypertension is one of the dreadful complications. We compared carvedilol with propranolol to find better drug that can prevent index variceal bleed in cirrhotic patients. 220 patients with known esophageal varices on upper GI endoscopy and no previous history of GI bleed were randomized to group A (Carvedilol) and group B (Propranolol). Bleeding occurred in 37.14% and 59.04% of the patients in group A (carvedilol) and B (propranolol) respectively (p=0.02). Bleeding was more common among patients with large as compared to small varices (67.04% versus 35.48% respectively). Among patients with large varices bleeding occurred in 58.13% and 75.55% of patients in group A and B respectively while in small varices, bleeding rate was 25% and 46.66% respectively (p=0.03). Regarding the response of beta blockers, mean pulse rate dropped from 85.15±5.49 to 59.8±2.39 per minute in Group A while in Group B it was reduced to 60.5±4.21 from 83.8±5.33 per minute at 3 years follow up. No significant difference found in the side effect profile. Our study showed that carvedilol was more effective than propranolol in primary prevention of variceal hemorrhage.

Keywords: Variceal Bleed, cirrhosis, effectiveness, primary prevention, non selective beta blockers (NSBBS), propranolol, carvedilol.

INTRODUCTION

Cirrhosis of the liver is ranked 12th among the prominent causes of death around the globe (Friedman 2013). The incidence of cirrhosis in viral hepatitis C (HCV), alcoholics, and non-alcoholic steatohepatitis (NASH) are all rising alarmingly. Besides the fact that viral hepatitis B (HBV) and HCV are the major causes of cirrhosis in developing countries, other causes like alcohol and autoimmune-related cirrhosis are on the rise as well (McCormick 2011). Portal hypertension is the underlying factor of numerous problems in individuals with liver cirrhosis, including esophageal varices, ascites, hepatorenal syndrome, hyperdynamic circulation, and hepatic encephalopathy. Upper gastrointestinal bleeding (UGIB) accounts for approximately 15% to 50% of the death rate in patients (Saltzman 2013). The prevalence of appearance and subsequent growth of gastroesophageal varices is around 7% per year after liver cirrhosis (Burroughs 2011). As the disease progressed, portal pressure rises which ultimately results in formation followed by rupture of varices. Hepatic venous pressure gradient (HVPG) exceeding 12 mmHg is a reliable predictor of esophageal varices haemorrhage (Ripoll et al 2007). One treatment option could be non-selective beta blockers (NSBB) with or without esophageal variceal band ligation (EVBL).

Keeping in view the complications caused by variceal bleeding, prevention of bleeding has become a primary concern for prevention against any adversity. The purpose of primary prevention is to avert variceal hemorrhage in patients with esophageal varices who do not have any previous history of UGIB. In patients with medium varices without red wale signs, NSBBs are preferred (Franchis and Baveno VI Faculty 2015). Among NSBB, carvedilol is favored for the reduction of portal pressure (Tripathi 2015).

Carvedilol, a non-selective β, and α-1 receptor-blocker proved to have a significant effect in lowering the portal pressure as compared to propanolol in both acute and chronic hemodynamic studies through various clinical trials (Tripathi 2007 & Cheng 2003). Carvedilol is composed of powerful nonselective β-receptors and weak α-1 receptor-blocking activity (Al-Shaqha 2009). As a β-receptor blocking drug, it proves to be 3-4 times more effective than propranolol (Karadsheh 2013 & Robertson 2018).

The hemodynamic response rate differs substantially for both carvedilol and propranolol administration with the former having a 58% rate and the latter having a 23% rate. Some recent studies have proved that carvedilol is more effective for the reduction of HVPG as compared to propranolol (Li 2011 & Reiberger 2013).

Until now, carvedilol has been used in clinical trials to prevent first variceal bleeding, yet it is not considered suitable for primary prevention by the food and drug authority (FDA). We intend to undertake a comprehensive

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trial with precise and meticulous patient selection and clinical outcomes along with the assessment of all the adverse effects before carvedilol can be advanced into evidence-based primary prevention of variceal bleeding.

MATERIALS AND METHODS

Study Design

This Quasi-experimental interventional comparative study was carried out in the Department of Medicine and Gastroenterology of 3 tertiary care centers in Lahore from 2014 to 2019. We included 220 patients, who had no past GI bleeding history. Patients aged between 18 & 75 years and with known varices small (grade 1-2) and large (grade 3-4) without red signs on upper GI endoscopy (EGD) were randomized to group A (Carvedilol) and group B (Propranolol) using lottery method Each patient was followed for 3 years for upper GI bleeding. The absence of variceal bleeding at 1 year and 3 years was considered an effective treatment response. Treatment compliance and side effects were noted during this period. Liver cirrhosis was diagnosed on clinical, biochemical, and radiological findings. History of illness and the clinical findings after examination were recorded and child Pugh scores were calculated while screening for enrolment.

Diagnostic procedures

The investigations performed were the complete blood count, liver and renal profile, coagulation profile, serum electrolytes, and abdominal sonography. Olympus® GIF 150 Gastroscope was used for endoscopy for variceal confirmation, graded as small or large, and presence or absence of red signs. Patients with acute liver failure, active alcoholism, hepatocellular carcinoma, chronic kidney disease, contraindications to endoscopy, and of beta-blockers (bradycardia <50 bpm, asthma, heart blocks, etc) and varices with red wale signs were excluded.

Data collection

Enrolled patients were divided into two equal groups (110 in each group) using a random table. 212 completed the study (107 in group A and 105 in group B). Tablet Carvedilol 3.125mg and tablet Propranolol 20mg were given to patients in group A and group B twice daily respectively. Each group was monitored monthly for three months, then quarterly for a year, and finally biannually for three years. At follow-up, the drug dose was titrated based on heart rate or the emergence of side effects, up to a maximum of propranolol 160 mg and carvedilol 25 mg daily. The desired heart rate was 60–70 beats per minute or a 25% fall from baseline was considered successful. Patients were questioned regarding hematemesis, melena, and pharmacological adverse effects during follow-up visits. For variceal surveillance, EGD was repeated at the 6th and 12th month for large and small varices respectively. Patients who bleed during treatment were considered treatment failures and were given standard treatment (i.e. EVBL plus β-blocker).

STATISTICAL ANALYSIS

Data was collected on a purposive excel sheet. Data validation and cleaning were performed on excel version 2016. Collected data were entered into SPSS version 22.0 and analyzed. Quantitative data like age, grade of varices, and child Pugh class are described with mean and standard deviation. Qualitative variables like gender, presence or absence of varices, variceal bleeding, obliteration of varices, compliance rate, and side effect profile of drugs were described as frequencies, tables, percentages, and proportions. The compliance rate was determined either by pill counting or supervised drug intake according to the patient's ease and non-compliance was questioned at each follow-up visit as per Performa. Chi square test was applied to compare presence or absence of bleeding. A P-value of less than 0.05 was considered significant.

Ethical approval

This study was approved by institutional review board (IRB Ref: 721/RC/KEMU) of institute. A written informed consent was taken from each patient willing to participate in study.

RESULTS

Variables, like demographics, etiology of liver disease, severity of liver disease, comorbidities, side effects, grade of varices and lost to follow up are shown in table 1. Total of 212/220 (96.36%) patients completed the study and 8/220 (3.63%) were lost to follow up. 53.30% were male (p= 0.03). Major cause of chronic liver disease (CLD) was HCV in both groups (161/212, 75.94%, p=0.07) (fig 1). In group A mean age was 53.86±5.62 which was comparable with mean age of group B 54.20 ±6.88 (p= 0.08). 99/212 (46.69%) were in Child Turcotte Pugh score (CTP) B whereas 37.13% and 16% were in CTP A & C respectively (p= 0.08) (table 1).

There were 103(48.58%) patients who had upper GI bleed while on NSBB with greater portion from propranolol group. 41 (37.14%) had UGIB in group A and 62 (59.04%) from group B. On the other hand, patients who did not had UGIB were 109 (51.41%), 66 (61.68%) from group A and 43 (40.95%) from group B respectively (*P*=0.02) at the end of three year follow up (table 3). No statistically significant difference found in results noted at 1year and 3 years follow up (table 2 & 3). No serious side effects were observed in either group. However, 47(22.16%) patients (21.49% in group A, 22.85% in group B) complained of minor events like fatigue, insomnia, nausea, pedal edema and nightmares (p= 0.19) (table 1).

Bleeding was more evident in patients with large varices with female gender and advance CTP (fig. 2&3). 124(58.49%) patients had small varices [64(59.81%) in group A and 60(57.14%) in group B] whereas 88(41.5%) had large varices [43(40.18%) in group A and 45(42.85%) in group B] (p=0.03). Among patients who had large varices, bleeding occurred in 59(67.04%) patients [25(58.13%) in group A and 34(75.55%) in group B] (p=0.01) while those who had small varices, bleeders were 44(35.48%), [16(25%) from group A and 28(46.66%) from group B] (p= 0.03) (table 3 & fig. 4).

8 patients (3 from group A, 5 from group B) lost to follow up, 4 exit the study due to side effects, 3 due to affordability issues and 1 want to try herbal treatment (table 1). Most of the patients (79.71%) were compliant with right dose of medicine intake and at right time, while 20.28% patients missed dose due to various reasons like cost, side effects and forgotten (p= 0.15) (table 1). In this study, considerable reduction in pulse rate observed in both groups, the mean value of initial pulse rate in group A was 85.15±5.49 per minute and in group B it was 83.8±5.33 per minute. On follow up at 3 years it was 59.8±2.39 per minute in group A while 60.5±4.21 per minute in group B (table 4).

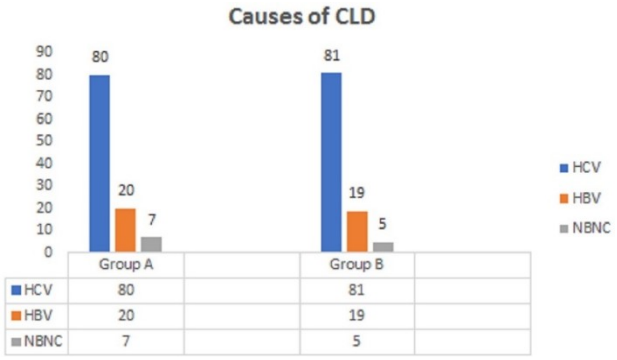

Fig. 1: Showing causes of chronic liver disease (CLD)

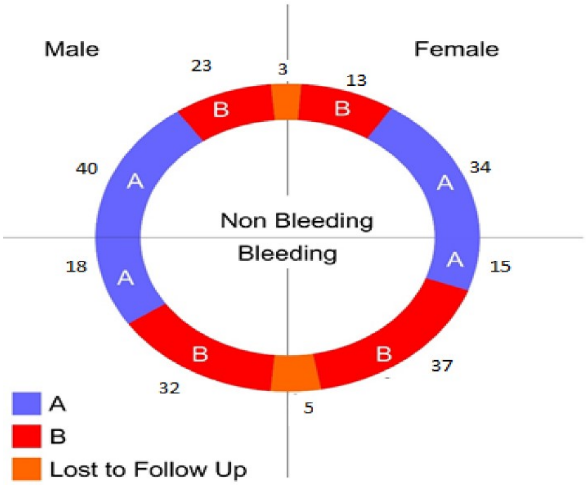

Fig. 2: Showing the bleeding status and loss to follow up in gender.

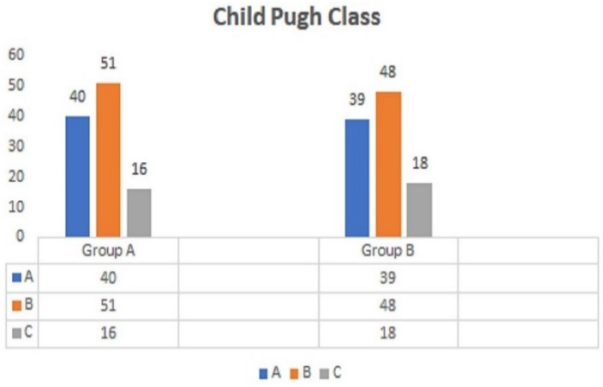

Fig. 3: Showing distribution of Child Torcotte Pugh score

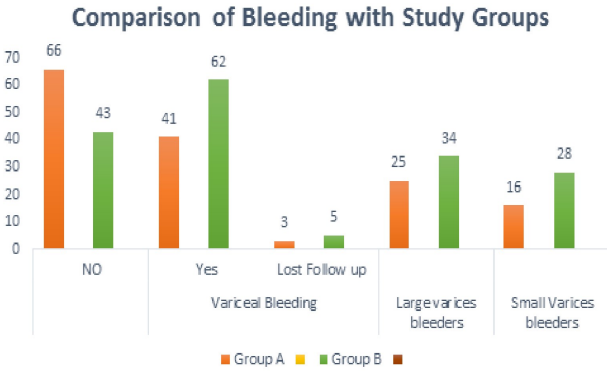

Fig. 4: Showing the bleeding status and loss to follow up in the study groups.

DISCUSSION

Nearly 50% of cirrhotic patients are diagnosed with esophageal varices, whereas bleeding from varices which accounts for a higher mortality rate in cirrhotic patients occurs in 33% of the patients. Chances of variceal bleeding highly depend upon the grade of varices and the extent of liver dysfunction. The appearance of varices and the severity of portal hypertension is correlated to the degree of fibrosis (Garcia-Tsao 2007).

The main aim of this study was to compare the effectiveness of carvedilol with propranolol to avert bleeding from varices in patients with cirrhosis. Side by side the possible adverse effects of these drugs on a group of patients were also taken into consideration. We found that carvedilol was 61.68% more potent than propranolol which had a prevention rate of just 40.95% against upper gastrointestinal bleeding in long term. This indicated that carvedilol has a better hemodynamic response as compared to propranolol. Carvedilol and propranolol had 37.14% and 59.04% variceal bleeding rates at the end of three years respectively. Hence, our study specified the importance of carvedilol being superior to propranolol in the prevention of variceal bleeding in cirrhotic patients thereby increasing their chances of survival following many RCTs published (Susana 2020).

Table 1: Demographic variables of study population (n = 220)

Variables	Group A n=110	Group B n=110	*P* value	Total n=220
Age (mean ±SD)	53.86 ±5.62	54.20 ±6.88	*0.082*	N/A
Gender Male	58 (54.2%)	55 (52.38%)	*0.03*	113 (53.30%)
Female	49 (45.79%)	50 (47.61%)		99 (46.69%)
Causes of CLD				
HCV	80(74.76%)	81(77.14%)	*0.072*	161(75.94%)
HBV	20(18.69%)	19(18.09%)		39(18.39%)
NBNC	07(6.5%)	05(4.76%)		12(5.66%)
Child –Pugh class				
A	40(37.38%)	39(37.14%)	*0.08*	79(37.31%)
B	51(47.66%)	48(45.71%)		99(46.69%)
C	16(14.95%)	18(17.14%)		34(16%)
Co-Morbities				
DM	06	03	*0.162*	09
HTN	04	03		07
Side effects				
Fatigue	14	11	*0.198*	25
Insomnia	01	05		06
Nausea	07	04		11
Pedal edema	1	02		03
Nightmares	0	02		02
Varices grade				
Small (grade 1-2)	64(59.81%)	60(57.14%)	*0.0351*	124
Large (grade 3-4)	43(40.18%)	45(42.85%)		88
Cause of lost to follow up				
Side effects	02	02	*0.001*	04
Affordability issues	01	02		03
Others	0	01		01
Compliance				
YES	86(80.37%)	83(79.04%)	*0.153*	169
NO	21(19.62%)	22(20.95%)		43
Cost	10	13		23
Side effects	08	04		12
Forgotten	03	05		08
CLD: chronic liver disease; HCV: hepatitis c virus; HBV: hepatitis b virus; NBNC: non hep B non hep C; DM, diabetes mellitus; HTN, hypertension.				

Table 2: Comparison of bleeding with study groups at 1 year

		Study Groups		p-value	Total
		A	B		
Variceal Bleeding	NO	67 (62.03%)	45 (42.85%)	0.026	108 (50.23%)
	YES	40 (37.38%)	60 (57.14%)		104 (48.37%)
	Lost follow up	03	05		08 (3.7%)
Large varices non-bleeders		19 (44.18%)	12 (26.66%)	*0.002*	31 (35.22%)
Large varices bleeders		24 (55.81%)	33 (73.33%)	0.017	57 (64.77%)
Small varices non-bleeders		48 (75%)	33 (55%)	0.011	81 (65.32%)
Small varices bleeders		16 (25%)	27 (45%)	0.034	43 (34.67%)

Table 3: Comparison of bleeding with study groups at 3 years.

		Study Groups		p-value	Total
		A	B		
Variceal Bleeding	NO	66 (61.68%)	43 (40.95%)	0.02	109(51.41%)
	YES	41 (37.14%)	62 (59.04%)		103(48.58%)
	Lost follow up	03	05		08 (3.7%)
Large varices non-bleeders		18(41.86%)	11 (24.44%)	*0.002*	29 (32.95%)
Large varices bleeders		25(58.13%)	34 (75.55%)	0.017	59 (67.04%)
Small varices non-bleeders		48 (75%)	32 (53.33%)	0.011	80 (64.51%)
Small varices bleeders		16 (25%)	28 (46.66%)	0.03	44 (35.48%)

Table 4: Comparison between pulse rates with study groups

Pulse Rates	Study Groups	Mean	SD	p-value
Initial Pulse Rate	A	85.15	5.49	0.267
	B	83.8	5.33	
Pulse Rate Month 1	A	82.15	5.27	0.371
	B	81.12	4.91	
Pulse Rate Month 2	A	79.4	4.08	0.185
	B	78.15	4.28	
Pulse Rate Month 3	A	76.87	4.49	0.662
	B	76.36	5.32	
Pulse Rate Month 6	A	75.52	4.49	0.104
	B	73.27	5.76	
Pulse Rate Month 9	A	71.23	5.16	0.723
	B	71.8	5.62	
Pulse Rate Month 12	A	69.5	3.35	0.610
	B	68.5	7.09	
Pulse Rate 2 years	A	61.2	3.90	0.332
	B	65.1	5.91	
Pulse Rate 3 years	A	59.8	2.39	0.192
	B	60.5	4.21	

22 deaths recorded from 2014 to 2019, of which 8 were because of variceal bleeding (five from the propranolol group and three from the carvedilol group). The main finding was that variceal bleeding did not occur in patients who continued the prescribed treatment in the majority of study patients. Whereas patients who stopped taking beta blockers were subjected to bleeding episodes. Also, carvedilol can be tolerated well with minimal side effects. Many patients achieved the desired heart rate with carvedilol 6.25mg twice daily dose whereas, in the propranolol group, it was achieved at 100-120mg daily dosing. Most of the side effects were reported on carvedilol 12.5mg (AM)+6.25mg (PM) and propranolol above 80mg daily. Hence, the optimal dose of carvedilol 6.25mg twice daily and propranolol up to 80mg daily may be desirable to avoid side effects.

Tong Li et al conducted a meta-analysis that comprised of 12 RCTs. A total of seven trials were conducted and the thermodynamic outcomes of carvedilol and propranolol were compared. It showed that carvedilol is associated with lower levels of HVPG in six months with MAP without falling further as compared to propranolol (Li T 2016). Three different studies were conducted that compared the outcomes of carvedilol and EVBL, the results of which showed that there were no substantial differences in mortality rate or variceal bleeding. Outcomes of carvedilol, nadolol, and isosorbide-5-mononitrate were compared in a trial which showed that there is no considerable difference in mortality or bleeding (Lo GH 2012). Another study analyzed carvedilol and nebivolol and demonstrated a greater reduction in HVPG in the previous group after 14 days of follow-up. For the primary and secondary prevention of variceal bleeding, carvedilol has been prioritized over other NSBBs by many other studies (Mo CY 2014, Sinagra 2014).

A non-randomized trial was conducted by Reiberger T et al that assessed carvedilol for primary prophylaxis of variceal bleeding in patients with cirrhosis having a thermodynamic nonresponse to propranolol. The data consisted of 104 patients that were followed up for two years having promising thermodynamic results in the above-mentioned group (Reiberger 2013).

Malandris K et al conducted a detailed analysis and reviewed carvedilol over other NSBBs including 13 trials. He found out carvedilol has more efficacy in the prevention of variceal bleeding. Also, the progression of varices can be delayed using carvedilol but this area needs more research (Malandris 2019).

CONCLUSION

For the primary prevention of variceal hemorrhage, our findings of this comparative interventional study of cirrhotic patients revealed that carvedilol was more effective than propranolol. Given the high bleeding rate despite the use of beta-blockers, we also recommend considering a combination of EVBL and beta blockers in patients with large varices without red signs. Also, no significant variations in the adverse effects imposed by medications on patients were identified in either group.

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