Original Article

# COMPARISION OF THE EFFICACY OF CARVEDILPL AND PROPRANOLOL IN THE SECONDARY PREVENTION OF ESOPHAGEAL VARICEAL BLEEDING

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**ABSTRACT:**

**Objective:**

The study was done to compare the efficacy of carvedilol and propranolol in the secondary prevention of upper gastrointestinal bleeding due to esophageal varices.

**Study Design:**

Randomized Controlled Trial

**Setting:**

Medical Unit II, Allied Hospital Faisalabad.

**Duration of Study:** 30th Jan, 2015 to 30th June, 2015.

**Sample Size:** Sample size was 94 as calculated by WHO sample size calculator

**Sampling Technique:**

Non-probability consecutive sampling

**Patients and Methods:** 94 patients presenting with upper GI bleed and having esophageal varices on endoscopy were included in the study. They were divided into two groups. Group A was given propranolol. Group B was given carvedilol. Doppler ultrasonography was done at the start of the study and at the end of the study. Paired
Sample T Test was applied to the portal vein diameter.

**Results** Mean portal vein diameter was 12.85±0.807cm at the start of the study and 11.04±0.808 cm at 24th week of study in Group A (P value = 0.00). Mean portal vein diameter was 12.77±0.633 cm at the start of the study and 11.49±0.953 cm at 24th week of study in Group B (P value = 0.00). Bleeding was effectively reduced in 35 patients (74.46%) in Group A and 35 patients (74.46%) in Group B (P value = 0.593).

**Key words**

Chronic liver disease, Esophageal Varices, Beta Blockers, Carvedilol, Propranolol.

## INTRODUCTION:

Cirrhosis of liver is a major worldwide health problem that causes significant morbidity and mortality. It is a major health issue in Pakistan also. Liver cirrhosis is a feared clinical consequence of continuous hepatocellular damage occurring because of a variety of causes especially chronic hepatitis B and C viral infections. The clinical features

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result from hepatic cell dysfunction, portosystemic shunting and portal hypertension.[1]

In Pakistan, the commonest cause of liver cirrhosis is chronic viral hepatitis. It is estimated that about 5-8% and 7-10% people in Pakistan are suffering from hepatitis B and C respectively.[2] Pakistan is home to approximately 10 million HCV infected people.[3] Of patients exposed to the hepatitis C virus, approximately 80% develop chronic hepatitis C[4] and of those, about 18.6% will develop cirrhosis over 20-30 years.[5] Of patients exposed to hepatitis B, about 3.8 to 12.4% develop chronic hepatitis B [6] and about 15% of those patients will go on to develop cirrhosis. International trials have shown that ten-year survival for decompensated liver cirrhosis is 7%.[7]

Portal hypertension is one of the major complications of liver cirrhosis. [8]. Variceal bleeding is one of the dreaded outcomes of portal hyoertension.[9] Ruptured gastroesophagealvarices are a frequent cause of upper gastreointestinal bleeding In patients suffering from liver cirrhosis. They account for 80% of all bleeding episodes. These episodes are associated with a mortality of 20% at 6 weeks.[10] Those who survive will rebleed within 6 months in up to 70% of cases.[11]Non-selective beta adrenergic blockers (propranolol ,nadolol) or prophylactic band ligation decrease absolute risk of variceal bleeding by approximately 10% per year and reduce mortality by almost 5%.[12]

Beta-blockers remain as first line therapy in patients with cirrhosis and large esophageal varices.[13] Propranolol is known to decrease portal pressure in cirrhotic patients with portal hypertension. However a substantial number of patients do not respond to propranolol administration.[14]Carvedilol is a non-selective beta blocker with alpha1 adrenergic blocking activity. It has been shown to decrease portal pressure in cirrhotic patients. Additionally, cavedilol has a greater portal hypotensive effect than propranolol alone in patients with cirrhosis.A study conducted by Malik et al at Sir Ganga Ram Hospital Lahore found that propranolol has greater efficacy as compared to cavedilol for the treatment of portal hypertension in cirrhotic patients ( 52% vs 24% ) [15]

Despite all efforts, mortality from bleeding gastroesophagealvarices is still high i-e up to 20%. In this study, we aim to compare the efficacy of propranolol and carvedilol in secondary prevention of upper gastrointestinal bleeding due to esophageal varices in cirrhotics with portal hypertension.

**OBJECTIVE:**

The study was done to compare the efficacy of carvedilol and propranolol in the secondary prevention of upper gastrointestinal bleeding due to esophageal varices.

**MATERIAL AND METHODS:**

**STUDY DESIGN:**

Randomized Controlled Trial

**Setting:**

Outdoor and Indoor Department Medical Unit II, Allied Hospital, Faisalabad.

**Duration of Study:**

6 months duration from 30th Jan 2015 to 30th June 2015

**Sample Size:**

Sample size was calculated by using WHO sample size calculator.
P1 = 52%
P2 = 24%
Power of study = 80%
Level of significance = 5%
Sample size = 47 patients in each group

**Sampling Technique:**

Non-probability consecutive sampling was used to enroll the patients.

**Sample Selection:**

Inclusion Criteria:

- Portal hypertension due to chronic liver disease
- Portal vein diameter more than 12mm on abdominal ultrasound done at Radiology Department Allied Hospital Faisalabad
- First time upper GI bleeding either as hematemesis or malena due to esophageal varices proven on endoscopy

Exclusion Criteria:

- Respiratory disease that contradict endoscopy
- Hepatic encephalopathy
- Hepatorenal Syndrome
- COPD or Asthma
- Treatment with vasoactive drugs within 1 week of inclusion
- Heart blocks that contradict treatment with beta-blocking agents
- Pregnancy

**DATA COLLECTION PROCEDURE:**

After taking approval from Ethical Review Committee, patients fulfilling the inclusion criteria were enrolled in the study. Informed consent was taken from each participant. Patients were divided into Group A and Group B using a computer generated random number table. 80 mg of propranolol was given to Group A for 12 weeks to achieve target pulse reduction. The doses was doubled weekly up to a maximum of 360 mg propranolol daily until target pulse reduction was achieved 6.25 mg of carvedilol was given to Group B for 12 weeks to achieve target pulse reduction. The doses were doubled weekly up to a maximum of 25 mg carvedilol daily until target pulse reduction was achieved. Data was collected through self conducted interviews using a standardized questionnaire. Information collected comprised age, sex, address, contact number, diameter of portal vein on abdominal ultrasound, number of upper GI bleeding episodes in 6 months after the start of study.

**DATA ANALYSIS PROCEDURES:**

All the collected information transferred to SPSS version 16 and analyzed accordingly. The quantitative variables like age, portal vein diameter and number of upper GI bleeding episodes were presented as mean and standard deviation. The qualitative variables like sex, were presented as frequency and percentage. Chi square test was applied to compare efficacy of drugs and paired sample t-test was applied to calculate efficacy of the two drugs. P value of ≤0.05 was considered as significant.

**RESULTS:**

94 patients were included in the study. Mean age of the study population was 50.14 $\pm$9.87 years. There were 46(48.9%) males and 48(51.1%) females (Fig. 1). Group A was given propranolol and Group B was given Carvedilol. Mean age in Group A was 51.19+9.575. IN this group, 25(53.2%) patients were males and 22(46.8%) patientswere female (Fig. 2). Mean age in Group B was 49.64+10.23. IN this group, 21(44.7%) patients were males and 26(55.3%) patients were females(Fig. 3).

Paired sample t-test was applied to portal vein diameter at the start of study and at 24$^{th}$ week of study. Mean Portal Vein Diameter was 12.85 $\pm$0.807 at start of study and 11.04$\pm$0.806 at 24$^{th}$ week of study in Group A (p-value=0.000). Mean Portal Vein Diameter was 12.77$\pm$ 0.633 at start of study and 10.49$\pm$ 0.953 at 24$^{th}$ week of study in Group B (p-value=0.000). (Table 1)

Bleeding was effectively reduced in 35(74.46%) patients in Group A and 35 (74.46 %) patients in Group B (p-value=0.593). (Table 2)

**Table –1 Mean Portal Vein Diameter In The Two Groups**

| | **Mean portal diameter in Group A (cm)** | **Mean portal vein diameter in Group B (cm)** |
|---|---|---|
| At start of study | 12.85$\pm$0.807 | 12.77$\pm$ 0.633 |
| After 6 months of study | 11.04$\pm$0.806 | 10.49$\pm$ 0.953 |
| Paired sample t-test (p value) | 0.000 | 0.000 |

**Table 2 Comparison Of Efficacy Of Drugs In The Two Groups**

| | | Treatment Group | | Total |
|---|---|---|---|---|
| | | Group A (Propranolol) | Group B (Carvedilol) | |
| Efficacy | Yes | 35 | 35 | 70 |
| | No | 12 | 12 | 24 |
| Total | | 47 | 47 | 94 |
| Chi Square Value | | 1.000 | | |
| p-value | | 0.593 | | |

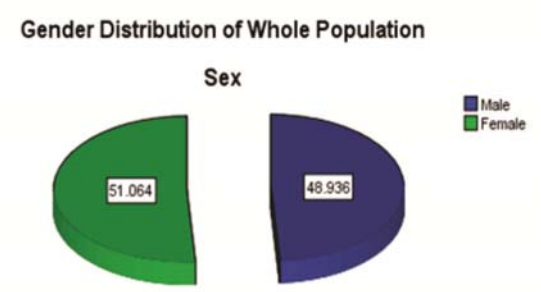


**Fig. 1-Gender Distribution of Whole Population**

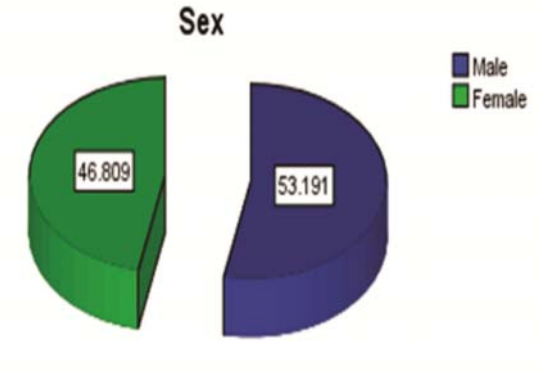


**Fig. 2. Gender Distribution of Group A**

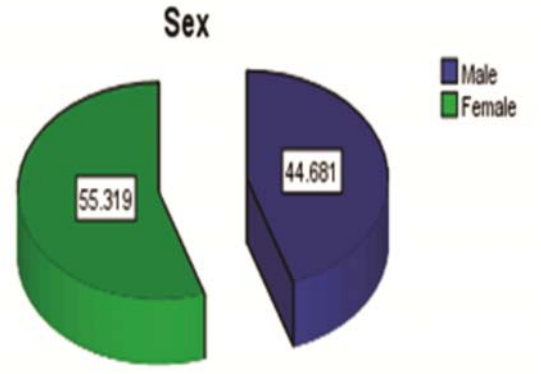


**Fig. 3Gender Distribution of Group B**

## DISCUSSION:

Portal hypertension is the main cause of morbidity and mortality in patients with cirrhosis. A portal pressure gradient, estimated by the hepatic venous pressure gradient HVPG) of 10 mmHg or more defines the presence of clinically significant portal hypertension (CSPH) and puts a patient at risk of clinical decompensation.[16,17] The HVPG threshold required for variceal bleeding is 12 mmHg.[18] Several longitudinal studies have demonstrated that if the HVPG decreases below 12 mmHg by means of pharmacological treatment[19] or spontaneously due to an improvement in liver disease,[20]variceal bleeding is totally prevented. Even if this target is not achieved, a substantial decrease in portal pressure from baseline levels (>20%) offers almost complete protection from variceal bleeding and decreases the risk of developing ascites, spontaneous bacterial peritonitis, hepatorenal syndrome, and death.[21] Current guidelines recommend using either a nonselective beta-adrenergic blocker (NSBB) or endoscopic band ligation (EBL) as firstline therapy for the prevention of first bleeding and a combination of NSBB and EBL as firstline therapy for the prevention of recurrent bleeding.[22]

Traditional NSBBs (nadolol, propranolol) reduce portal pressure by decreasing portal venous inflow, portocollateral blood flow,[23] and variceal pressure.[24] The decrease in splanchnic blood flow is the result of a decrease in cardiac output due to the blockade of cardiac beta-1 adrenoceptors, and of splanchnic

vasoconstriction due to the beta-2 receptor blockade, that in turn leads to unopposed alpha-adrenergic activity.[25]

Carvedilol further enhances the NSBB mechanism of action by adding in a mild intrinsic alpha-1-adrenergic blocker effect. This alpha-blockade leads to a reduction in hepatic vascular tone and hepatic resistance. In keeping with this multifaceted blockade, several studies have confirmed that there is a greater decrease in portal pressure with carvedilol than propranolol, both acutely and chronically.[26,27] In addition, a recent study from Austria demonstrated that 56% of the patients not achieving a sufficient hemodynamic response to propranolol responded to carvedilol.[27]

Our study comprised of 94 subjects, done over a period of six months in outdoor/indoor patient setting. The two drug classes were found effective for preventing esophageal variceal bleeding in portal hypertension. They had an equivalent effect on the end point that was preventing recurrence of esophageal variceal bleed.This study indicates that propranolol and carvedilol have equivalent efficacy in providing decrease in portal pressure and thereby decreasing overall recurrence of esophageal variceal bleed. This result is consistent with the emerging data that support the clinical equivalence of propranolol and carvedilol as compared to the previous popular concept supporting carvedilol over propranolol. [27,28]

A study was published in Scandinavian Journal of Gastroenterology in 2012 comparing the long term effect of carvedilol and propranolol in reducing hepatic venous pressure gradient. It concluded that carvedilol is at least as effective as propranolol in reducing HVPG after long term administration.[29]

There was a poster presentation by Gonzaler et al in 2011that directly compared the effect of propranolol and carvedilol in treatment of esophageal varices due to portal hypertension. It concluded that although carvedilol is superior to propranolol in reducing portal hypertension. Its overall hypotensive effect might preclude its use. Furthermore, the lack of clinical endpoints that would impact survival and mortality necessitates further investigation.[30]

Banaresand colleagues studied propranolol and carvedilol in patients with esophageal varices in portal hypertension. They concluded that the target in the pharmacological treatment of portal hypertension would be to reduce the HVPG by at least 20% of baseline values and preferably below 12 mm Hg. Long term carvedilol treatment in patients with cirrhosis and esophageal varices decreases portal pressure more than propranolol and induces more frequently a beneficial hemodynamic response. [31,32]

In another study by Banares et al in 2002, it was concluded that carvedilol has a greater portal hypotensive effect than propranolol in patients with cirrhosis. However, its clinical applicability may be limited by its systemic hypotensive effects. Further trials are needed to confirm the therapeutic potential of carvedilol.[33]

This recommendation is in contrast to our study in which we have found that propranolol and carvedilol both have equivalent efficacy and their effect on mortality is equal in long term.

Pitfalls of our studyare:

- Small sample size
- No double binding was done

Large randomized controlled trials are needed to further validate these results.

## CONCLUSION:

It has been concluded from this study that propranolol and carvedilol both significantly reduce potal venous pressure and there is no statistically significant difference in efficacy of these two drugs in decreasing portal pressure and thus reducing recurrence of esophageal variceal bleed.

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| 2 | Aamir Husain | Data Collection<br>Online search |
| 3 | Muhammad Waqas Fatima Hanif | Article and undertaking name change |

O son of Adam, when you see that your Lord, the Glorified, bestows His Favors on you while you disobey Him, you should fear Him (take warning that His Wrath may not turn those very blessings into misfortunes).

***Hazrat Ali (Karmulha Wajhay)***