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A RANDOMIZED CLINICAL TRIAL TO COMPARE THE EFFICACY OF PROPRANOLOL AND CARVEDILOL FOR TREATMENT OF PORTAL HYPERTENSION IN LIVER CIRRHOSIS

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Abstract:

Aim of Study: *The aim of our study was to compare the efficacy of different doses of propranolol and carvedilol for treatment of portal hypertension in patients of liver cirrhosis.*

Study Design: *A randomized clinical trial.*

Place and Duration: *We conducted this study for the duration of one year in medical department of Services hospital, Lahore for the duration of six months from 1st December, 2019 to 30th May, 2020.*

Methodology: *After ethical approval of the study, 100 confirmed cases of liver cirrhosis with portal hypertension of ages 16 to 85 years with either gender were selected for this study by non-probability purposive sampling. These cases were randomly named as group A (I), A (II) & B (I), B (II). In group A (I) & (II) patients were given propranolol (20mg), Carvedilol (6.25mg) and group B (I) & (II) patients were given propranolol (40mg), carvedilol (12.5mg). Portal hypertension was labeled as portal flow velocity >12cm H2O/sec on Doppler ultrasonography. Portal flow velocity (PFV) was measured before and 90 minutes after administration of trial drugs and >20% decrease in portal flow velocity from baseline was considered as efficacy.*

Results: *The mean age of the patients in group A was 48±14.4 years and in group B was 54 ±12.4 years. In group A (I), the mean portal flow velocity at baseline was 22.16±4.28 cm H2O/sec and after treatment at 90 minutes mean portal velocity was 18.12±4.14 cm H2O/sec. In group A (II), the mean portal flow velocity at baseline was 25.16±4.2 and after treatment at 90-minute mean portal velocity was 13.16±2.42. In group B (I), the mean portal flow velocity at baseline was 25.56±3.54 and after treatment at 90 minutes it was 13.96±3.5.In group B (II), the mean portal flow velocity at baseline was 28.44±4.13 and In group B (I) after treatment at 90 minute mean portal velocity was 10.36±2.49.*

Conclusion: *At the end of our trial we observed that high dose carvedilol was more effective than propranolol as well as low dose of carvedilol in reduction of PFV.*

Keywords: *Liver Cirrhosis, Carvedilol, Portal Flow Velocity, Portal hypertension, Propranolol.*

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INTRODUCTION:

Liver cirrhosis is the consequence of hepato-cellular injury that leads to both fibrosis and nodular regeneration in the liver. It is the most common cause of portal hypertension and its morbidity and mortality is higher in our country. Clinically its presents as a result of hepatocellular dysfunction, ascites and portal hypertension [1,2]. In Pakistan, chronic viral hepatitis B & C is the commonest cause of liver cirrhosis with approximately 5-8% and 7- 10% patients with hepatitis B and C respectively [3]. The annual incidence rate is around 14–26 per 100,000 inhabitants and approximately 170,000 people die from complications of cirrhosis per year [4].

One of the major complications of liver cirrhosis is portal hypertension [5,6]. Variceal upper gastroesophageal bleeding is one of the dreaded outcomes of portal hypertension [7,8]. It constitutes 80% of all bleeding episodes, associated with 20% mortality at 6 weeks [9]. Annual variceal bleeding risk reduction with non- selective β-adrenergic blockers (propranolol, nadolol) or prophylactic band ligation is around 10% and mortality reduction is almost 5% [9]. Beta blockers are first line treatment in esophageal varices [10]. Propranolol is used to decrease portal pressure in cirrhotic portal hypertension however a small number of patients do not respond to propranolol therapy [11].

Carvedilol is another nonselective β-blocker with α_1-adrenergic blocking activity that is used to decrease portal pressure with better effect [12]. Despite all the therapeutic options, mortality from bleeding gastrointestinal varices due to portal hypertension is up to 20% so we still need to ascertain the most effective treatment, so the rationale for this study is to compare propranolol and carvedilol to find an effective treatment of portal hypertension.

METHODOLOGY:

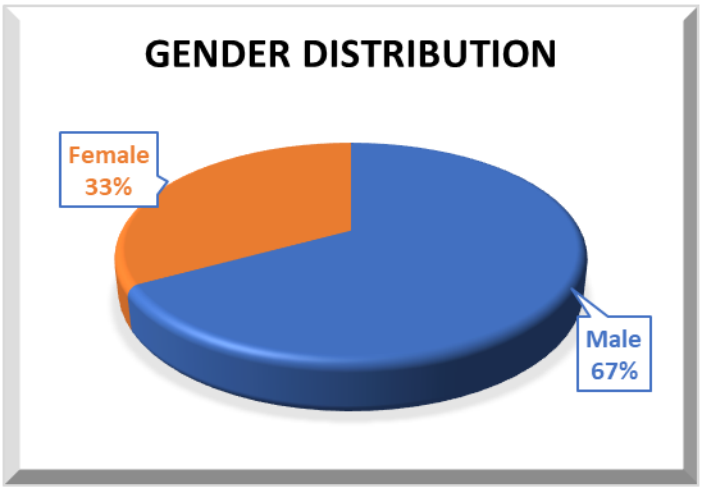
This randomized clinical trial was conducted in the medical department of Services hospital, Lahore for the duration of six months from 1st December, 2019 to 30th May, 2020. After ethical approval of the study, 100 confirmed cases of liver cirrhosis with portal hypertension of ages 16 to 85 years with either gender were selected for this study from outpatient & indoor departments by nonprobability purposive sampling. Major exclusions of the study were patients of Peripheral vascular disease, Congestive cardiac failure, Cerebrovascular accident, Non cirrhotic portal hypertension, Severe chronic obstructive airway disease or Asthma, hepato-renal failure, diabetes mellitus, Liver Malignancy & encephalopathy, Postural hypotension, Dehydration, Hyponatremia, pregnancy & Concomitant use of β -blocker & Calcium channel blocker. An informed written consent was taken from the patients. Demographic data (age, sex, address) was recorded and patients were categorized accordingly. The patients were randomly divided into group A & B by lottery method, further group A & group B were divided in to A (I) and A (II); group B (I) and B (II). Group A (I) patients were given propranolol (20 mg) and group A

(II) were given carvedilol (6.25 mg). Group B (I) patients were given Propranolol (40 mg) and B (II) were given carvedilol (12. 5mg). Portal flow velocity was measured before and 90 minutes after the administration of the above-mentioned drugs by a radiologist on doppler ultrasonography and more than 20% decrease was considered as efficacy. If during 90 minutes if any complication occurred in any patient then it was excluded from the study and managed accordingly. Data was analyzed by software SPSS version 16. The quantitative variables like age were presented as mean and standard deviation. The qualitative variables like sex, causes of liver cirrhosis were presented as frequency and percentages. Analysis of variance test (ANOVA) was applied to compare the statistical significance between different doses of all four (AI, AII, BI, BII) independent groups. Data was stratified for drugs significance in cirrhosis (portal hypertension). P value of ≥0.05 was taken as significant.

RESULTS:

The mean age in group-A was 48±14.4 years and in group-B was 54 ±12.4 years. In group-A, there were 40 (80%) male and 10 (20%) female patients and similarly in group-B, there were 27 (54%) male and 23 (46%) female patients.

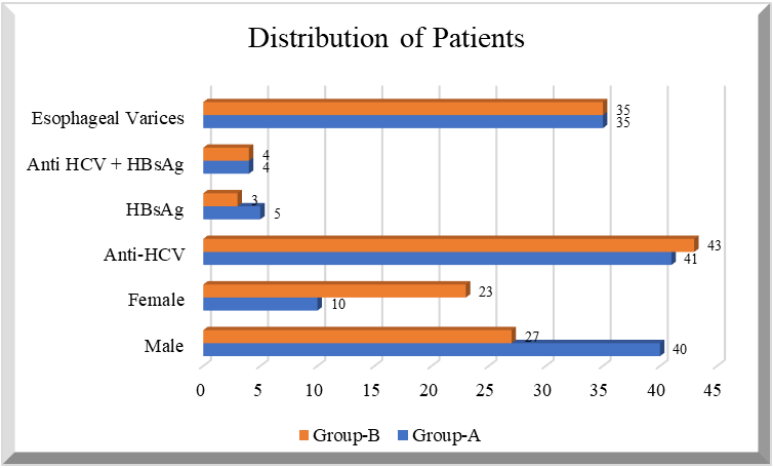
Fig No 01: Gender Distribution



In group A, there were 41 (82%) patient anti HCV positive, 5 (10%) HBsAg positive & 4 (8%) were both Anti HCV + HBsAg positive. In group B, there were 43 (86%) patient anti HCV positive, 3 (6%) HBsAg positive & 4 (8%) both Anti HCV + HBsAg positive. In group A, there were 35 (70%) patients who presented with esophageal varices. In group B, there were 35 (70%) patients who presented with esophageal varices (Table 1).

Table No 01: Distribution of Patients by Age in A & B Groups

Preferences	Group-A	Group-B
Age (years)	48±14.4	54±12.4
Male	40	27
Female	10	23
Anti-HCV	41	43
HBsAg	05	03
Anti HCV + HBsAg	04	04
Esophageal Varices	35	35
Each group quantity	50	50



In group A (I), the mean portal flow velocity at baseline was 22.16±4.28 cmH_2O/sec and after treatment at 90 minutes mean portal velocity was 18.12±4.14 cm H_2O/sec. The minimal portal flow velocity in group A (I) was 16 cm H_2O/sec and maximum was 29 cm H_2O/sec. After 90 minute of drugs administration minimal portal flow velocity recorded

was 12 cm H_2O/sec and maximum was 26 cm H_2O/sec. In group A (II), the mean portal flow velocity at baseline was 25.16±4.2 and after treatment at 90 minute mean portal velocity was 13.16±2.42. The minimal portal flow velocity in group A (II) was 19 cmH_2O/sec and maximum was 32. After 90 minute of drugs administration minimal portal flow velocity recorded was 09 cm H_2O/sec and maximum was 19 cm H_2O/sec (Table 2).

Table No 02: Comparison of Portal Flow Velocity (PFV) at Baseline and After 90 Minutes of Low Dose of Drugs (Propranolol & Carvedilol)

Statistics	Group A (I)		Group A (II)	
Pfv	**Before**	**After**	**Before**	**After**
Total	25	25	25	25
Mean	22.16±4.29	18.12±4.15	25.16±4.20	13.16±2.43
p-value	0.001		<0.0001	

In group B (I), the mean portal flow velocity at baseline was 25.56±3.54 and after treatment at 90 minutes it was 13.96±3.5. The minimal baseline portal flow velocity was 19cm H_2O/sec and maxi- mum was 32. After 90 minute of drugs administration minimum portal flow velocity was 8 and maximum was 20. In group B (II), the mean portal flow velocity at baseline was 28.44±4.13 and In group B (I) after treatment at 90 minute mean portal velocity was 10.36±2.49. The minimal portal flow velocity in group B (II) was 19 cm H_2O/sec and maximum was 35. After 90 minutes of drugs administration portal flow velocity recorded was, minimum 6 and maximum 17cm H_2O/sec (Table 3).

Table No 03: Comparison of Portal Flow Velocity (PFV) at Baseline and After 90 Minutes of High Dose of Drugs (Propranolol & Carvedilol)

Statistics	Group B (I)		Group B(II)	
Pfv	**Before**	**After**	**Before**	**After**
Total	25	25	25	25
Mean	25.56±3.55	13.96±3.52	28.44±4.13	10.36±2.50
p-value (Ind T-test)	<0.0001		<0.0001	
P-Value (ANOVA)	<0.0001 (F-test = 159.319)			

DISCUSSION:

In this study the mean age of the patients in group A was 48±14.4 years and in group B was 54 ±12.4 years. In this study, there were 40 (80%) male and 10 (20%) female patients in group-A and in group B, there were 27 (54%) male and 23 (46%) female patients.

In group A (I), the mean portal flow velocity at baseline was 22.16±4.28 and after treatment at 90 minutes was 18.12±4.14. In group A (II), the mean portal flow velocity at baseline was 25.16±4.2 and after treatment at 90 minutes it was 13.16±2.42. In group B (I), the mean portal flow velocity at baseline was 25.56±3.54 and after treatment at 90 minutes it was 13.96±3.51. In group B (II), the mean portal flow velocity at baseline was 28.44±4.13 and after treatment at 90 minutes it was 10.36±2.49. In this study Carvedilol seems to be more effective than propranolol and high dose of carvedilol is more effective than propranolol as well as low dose carvedilol. The better efficacy in primary prevention of variceal bleeding suggests its role in treatment of portal hypertension [11,13,14].

Recently, a non-randomized study including 104 participants with a follow-up of 2 years had assessed the efficacy of carvedilol for propranolol non-responders [15].

It was reported that a significant proportion of propranolol non-responders could achieve haemodynamic responses to carvedilol treatment. In addition, the variceal bleeding rate, hepatic

decompensation rate and mortality rate were significantly decreased in the haemodynamic response group. This study indicated that carvedilol might be better than propranolol in decreasing the hepatic venus pressure gradient (HVPG) and improving the survival of patients with cirrhosis [16].

CONCLUSION:

Both drugs have significant effect in lowering portal flow velocity, but carvedilol (6.25mg, 12.5mg) was more effective than propranolol (20mg, 40mg) in lowering portal flow velocity, as a treatment of portal hypertension in patients of Chronic Liver Disease. Therefore, higher doses of carvedilol can be used for better control of portal hypertension in patients of chronic liver disease.

REFERENCES:

1. Brunicardi F, Andersen D, Billiar T, Dunn D, Hunter J, Matthews J, et al. Schwartz's principles of surgery: McGraw-hill; 2014.
2. Asrani SK, Larson JJ, Yawn B, Therneau TM, Kim WR. Underestimation of liver-related mortality in the United States. Gastroenterology 2013;145(2):375- 82. 40-2
3. Mokdad AA, Lopez AD, Shahraz S, Lozano R, Mokdad AH, Stanaway J, et al. Liver cirrhosis mortality in 187 countries between 1980 and 2010: a systematic analysis. BMC Med 2014;12(1):145.
4. Pinter M, Trauner M, Peck-Radosavljevic M, Sieghart W. Cancer and liver cirrhosis: implications on prognosis and management. ESMO Open 2016;1(2)30-2.
5. Sauerbruch T, Schierwagen R, Trebicka J. Managing portal hypertension in patients with liver cirrhosis. F1000 Res 2018; 7: F1000.
6. Tetangco EP, Silva RG, Lerma EV. Portal hypertension: Etiology, evaluation, and management. Dis Mon 2016;62(12): 411-26.
7. Tantau M, Crisan D, Popa D, Vesa S, Tantau A. Band ligation vs. N-Butyl-2-cyanoacrylate injection in acute gastric variceal bleeding: a prospective follow- up study. Annals of hepatology 2014;13(1): 75-83.
8. LaBrecque D, Khan A, Sarin S, Le Mair A. Esophageal varices. World Gastroenterol Organ Glob Guidel 2014; 2014:1-14.
9. Haq I, Tripathi D. Recent advances in the management of variceal bleeding. Gastroenterol Rep 2017;5(2):113-26.
10. Burza MA, Marschall H-U, Napoleone L, Molinaro A. The 35-year odyssey of beta blockers in cirrhosis: any gender difference in sight? Pharmacological research 2017; 119:20.
11. Sinagra E, Perricone G, D'Amico M, Tine F, D'Amico G. Systematic review with meta-analysis: the haemodynamic effects of carvedilol compared with propranolol for portal hypertension in cirrhosis. Alimentary pharmacology & therapeutics 2014;39(6):557-68.
12. Gluud LL, Krag A. Banding ligation versus beta-blockers for primary prevention in esophageal varices in adults. Cochrane Database Syst Rev 2017(8): CD004544.
13. Hobolth L, Bendtsen F, Hansen EF, Møller S. Effects of carvedilol and propranolol on circulatory regulation and oxygenation in cirrhosis: a randomized study. Digestive and Liver Disease 2014; 46(3):251-6
14. Collins P, Ayres L, Valliani T. Drug therapies in liver disease. Clinical Medicine 2013; 13(6):585-91.
15. Reiberger T, Ulbrich G, Ferlitsch A, Payer B, Schwabl P, Pinter M, et al. Vienna Hepatic Hemodynamic Lab. Carvedilol for primary prophylaxis of variceal bleeding in cirrhotic patients with haemodynamic non-response to propranolol. Gut 2013; 62(11): 1634-41.
16. Li T, Ke W, Sun P, Chen X, Belgaumkar A, Huang Y, et al. Carvedilol for portal hypertension in cirrhosis: systematic review with meta-analysis. BMJ Open 2016; 6(5):24-6.