Effect of Acute Administration of Propranolol, Carvedilol, ISO-Sorbide Dinitrate, "Propranolol Plus ISO-Sorbide Dinitrate" and "Carvedilol Plus ISO-Sorbide Dinitrate" on Portal Venous Pressure.

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ABSTRACT

Pharmacotherapy of portal hypertension in patients with cirrhosis includes beta-blockers, nitrates, somatostatin analogues, alpha-blockers like prazosin. These drugs differ widely in their effectiveness, adverse effects and patient compliance. Beta-blockers particularly propranolol are the most commonly used drugs. Of late, carvedilol has been used and found to be superior to propranolol. The present study was aimed at assessing the effect of propranolol, carvedilol, iso-sorbide dinitrate; combination of "propranolol and iso-sorbide-dinitrate" and carvedilol and isosorbide dinitrate" on portal venous pressure in cirrhosis of liver. 40 consecutive patients with cirrhosis were subjected to hepatic venous catheterization. Baseline free and wedged hepatic venous pressures were recorded. Patients were randomly assigned to receive propranolol 40 mgm PO (n=8); carvedilol 25mg PO (n=8); iso-sorbide dinitrate 20 mg PO (n=8); propranolol plus iso-sorbide dinitrate (40 mg and 20 mg) (n=8) and carvedilol plus iso-sorbide dinitrate (25 mg and 20 mg PO) (n=8). Hemodynamic values were repeated 90 minutes after drug administration. All drugs significantly decreased the hepatic venous pressure gradient. Combination of carvedilol and iso-sorbide dinitrate was found to be most effective. The mean $\pm$ SD drop in hepatic venous pressure gradient was: propranolol 4.3 ± 1.4 mmHg (27%); Carvedilol 4.4 ± 1.8 mmHg (30%); iso-sorbide dinitrate 2.8 ± 1.4 mmHg (17%); propranolol plus iso-sorbide dinitrate 5.1 ± 1.0 mmHg (31%) and "Carvedilol plus iso-sorbide dinitrate" 5.5 ± 1.2 mmHg (36%). Conclusion: combination of carvedilol and iso-sorbide dinitrate is the most effective anti portal hypertensive regimen in patients of cirrhosis. JMS 2013; 16(2):80-85

Key words:- Cirrhosis, portal hypertension, hepatic venous catheterization, hepatic venous pressure gradient, portal venous pressure.

INTRODUCTION

The pharmacologic treatment of portal hypertension is recognized as an important therapeutic option for primary and secondary prophylaxis of variceal bleeding.¹ Vasoactive drugs mainly non-selective beta-blockers and nitrates, have been found to decrease the hepatic venous pressure gradient (HVPg) in a significant number of cirrhotic patients.

Lebre et al were the first to report that continuous administration of propranolol effectively reduced portal pressure² and prevented recurrent variceal bleeding in

patients with cirrhosis.³ Its efficacy has been clearly proven for the prevention of first variceal bleeding^{4,5} and rebleeding.^{6,7}

Nitro-vaso dilators (iso-sorbide mono-nitrate and iso-sorbide dinitrate) have been found to be effective in reducing portal venous pressure.⁸ These drugs enhance the portal pressure reducing effects of beta-blockers by reducing the porto-hepatic vascular resistance.^{9,10} Iso-sorbide mononitrate has been used either alone or in combination with propranolol for treatment of portal hypertension/variceal bleeding.¹¹ Of late, the non-selective beta-blocker, "carvedilol", having intrinsic adrenergic blocking activity has been introduced in the treatment of portal hypertension. Han-chie-Lin et al compared the efficacy of carvedilol with a combination of "propranolol and iso-sorbide dinitrate". They found that carvedilol was more effective than "propranolol plus iso-sorbide dinitrate"

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in the reduction of HVPG.¹² The present study was conducted in the departments of Gastroenterology and Cardiology, SKIMS, Srinagar, India to assess the effects of propranolol, carvedilol, iso-sorbide dinitrate, combination of propranolol plus isosorbide dinitrate and carvedilol plus isosorbide dinitrate on portal venous pressure in patients with cirrhosis of liver.

METHODS

The study was conducted on 40 patients of cirrhosis of liver with esophageal varices. Diagnosis of cirrhosis was made on the basis of unequivocal clinical, biochemical and ultrasonographic findings. The study protocol was approved by the ethical committee of our hospital. All patients gave written consent to participate after a complete explanation of the purpose of the study. There were 23 men and 17 women with a mean age of 43 ± 11 years. Nineteen patients had history of variceal bleeding and 20 had ascites. Additional clinical information on the patients is given in table 1. Liver biopsy was done wherever found necessary in cases having no clinical signs of decompensated cirrhosis and portal hypertension (ascites, varices, encephalopathy). All patients had an upper GIT endoscopy to assess the presence of esophageal or gastric varices. The severity of liver dysfunction was determined according to the "Child-Pugh-Turcot" scoring system. No patient was receiving vasoactive drugs at the time of study.

Hemodynamic Study: After overnight fast, all patients underwent hepatic venous catheterization, as described by Groszmann et al, through the right femoral route with a 7F Swan Ganz catheter (Arrow Balloon Wedge Pressure Catheter A1-07127) by using the Selidinger technique in supine position under 2% local xylocaine (10ml). The catheter was placed into the right hepatic vein under fluoroscopic guidance. Free hepatic venous pressure (FHVP) was recorded approximately 3-4 cms away from the IVC. Then the catheter was advanced ahead and its balloon was inflated. 1 ml of contrast was injected to confirm wedging. Wedged hepatic venous pressure (WHVP) was recorded when no dye leaked back. Portal pressure was estimated as the HVPG (difference between WHVP and FHVP). The pressures were recorded on monitor (AX10M-ARTIS cine angiographic system-

Siemens) and a pressure tracing obtained. All pressures were taken in duplicate and final results were given as arithmetic mean of the two readings. The balloon was deflated and kept in position.

Study protocol: After completing baseline hemodynamic measurements, the patients randomly received propranolol 40mg (n=8), carvedilol 25mg (n=8), isosorbide dinitrate 20mg (n=8), combination of propranolol 40mg and isosorbide dinitrate 20mg (n=8) or combination of carvedilol 25mg and isosorbide dinitrate 20mg (n=8) orally and the hemodynamic measurements were repeated 90 minutes later.

Statistical method used:

The results were expressed as mean $\pm$ SD. Statistical analysis was done with SPSS 10.0 package (SPSS, Chicago, IL). To assess the significance of comparisons with baseline within each group, student's t-test was used. The contribution of each pharmacological agent or combination of agents was estimated by the relative effect with 95% confidence intervals (CIs). Significance was established at $p < 0.05$.

RESULTS

All patients had moderate to severe portal hypertension as shown by HVPG above 12 (except in 4 patients whose HVPG was < 12 mmHg (one each in Propranolol, Carvedilol, "Propranolol + Isosorbide dinitrate" and "Carvedilol + Isosorbide dinitrate" groups) and by the presence of esophageal varices and other complications of portal hypertension (Table I). The 5 groups of patients were similar with regards to baseline HVPG and clinical characteristics.

The splanchnic hemodynamic values before and 90 min after drug administration are depicted in Table II.

Effects of Propranolol:

90 minutes after the oral intake of propranolol, there was a reduction in HVPG (from 15.3 ± 3.8 to 11.0 ± 3.9 mmHg: $p < 0.001$. The range of fall was 2-6 and 95% CI was 3.1-5.4. The magnitude of fall in HVPG was -27%; mean fall 4.3 ± 1.4 mmHg.

Effects of Carvedilol:

Carvedilol (25mg) caused a significant fall in HVPG after

Table I: Clinical Characteristics of the patients and their basal HVPG

Parameter	Propranolol (n=8)	Carvedilol (n=8)	Isosorbide Dinitrate (n=8)	Propranolol + Isosorbide Dinitrate (n=8)	Carvedilol + Isosorbide Dinitrate (n=8)	P value
Age (yrs) Mean $\pm$ SD	41.63 $\pm$ 11.95	45.75 $\pm$ 16.96	40.13 $\pm$ 14.62	46.88 $\pm$ 13.94	41.50 $\pm$ 17.83	0.82 (NS)
Sex						
Male	4	6	5	5	4	(NS)
Female	4	2	3	3	4	
Etiology						0.81 (NS)
HBV	2	2	2	1	2	
HCV	1	X	1	1	1	
Alcohol	X	1	X	1	X	
Others	X	1	X	X	X	
Un-defined	5	4	5	5	5	
Previous Ascites	4	3	4	5	4	(NS)
Esophageal varices	6	5	5	6	7	(NS)
Pre. Variceal bleeding	3	4	3	4	5	(NS)
Encephalopathy	X	X	X	X	X	
Child-Pugh class						0.58 (NS)
A	5	3	3	2	2	
B	2	3	3	3	3	
C	1	2	2	3	3	
Basal HVP GmmHg	15.3 $\pm$ 3.8	14.4 $\pm$ 3.6	15 $\pm$ 2.7	16 $\pm$ 3.9	16.23 $\pm$ 3.7	

Table II: Hemodynamic events at baseline and at 90 minutes after drug administration

Drug	FHVP		WHVP		HVPG	
	Basal	At 90 min	Basal	At 90 min	Basal	At 90 min
Propranolol	6.8 $\pm$ 1.8	5.3 $\pm$ 2.1	21.9 $\pm$ 3.5	16.3 $\pm$ 3.2	15.3 $\pm$ 3.8	11.00 $\pm$ 3.9
Carvedilol	4.3 $\pm$ 2.1	4.9 $\pm$ 2.1	18.5 $\pm$ 4.1	14.8 $\pm$ 3.0	14.4 $\pm$ 3.6	10.0 $\pm$ 3.5
Isosorbide Dinitrate	4.0 $\pm$ 1.6	3.1 $\pm$ 2.2	19.6 $\pm$ 3.9	16.0 $\pm$ 2.7	15.6 $\pm$ 2.7	12.9 $\pm$ 2.0
Propranolol + Isosorbide Dinitrate	5.0 $\pm$ 2.3	4.8 $\pm$ 2.0	21.8 $\pm$ 3.8	16.4 $\pm$ 1.9	16.8 $\pm$ 3.9	11.8 $\pm$ 3.6
Carvedilol + Isosorbide Dinitrate	5 $\pm$ 1.8	4.37 $\pm$ 2.1	21.12 $\pm$ 3.5	15.3 $\pm$ 3.2	16.12 $\pm$ 3.7	10.63

90 minutes (from 14.4 $\pm$ 3.6 to 10.0 $\pm$ 3.6 to 10.0 $\pm$ 3.5 mmHg $p < 0.001$). The range of fall was 8, CI-2.8-5.9 and magnitude of fall was -30%, mean fall 4.4 $\pm$ 1.8 mmHg.

Effect of Isosorbide dinitrate:

Oral administration of 20mg Isosorbide dinitrate led to a fall in HVPG (from 15.6 $\pm$ 2.7 to 12.9 $\pm$ 2 mmHg; $P < 0.001$) after 90 minutes. The range of fall was 2-6; 95% CI-1.6-3.9; magnitude of drop-17%. Mean fall 2.2 $\pm$ 1.4 mmHg.

Effect of “propranolol plus Isosorbide dinitrate”

The oral administration of 40mg propranolol together with

20mg Isosorbide dinitrate at the end of 90 minutes caused reduction in HVPG (from 16.8 $\pm$ 3.9 to 11.8 $\pm$ 3.6; $p < 0.0001$) range of fall 4-7; 95% CI-4.4-6.1 and percent fall of -31%. Mean fall 5.0 $\pm$ mmHg.

Effects of “Carvedilol Plus Isosorbide Dinitrate”

The combination of carvedilol (25mg) and Isosorbide-dinitrate (20mg) when given orally caused a drop in HVPG from 16.3 $\pm$ 3.8 to 10.0 $\pm$ 3.9 mmHg; $p < 0.0001$. The range of fall in HVPG was 4-7; 95% CI-4.5-6.5 and percent drop was -36. Mean drop 5.5 $\pm$ 1.2 mmHg (Table III)

Table III: Fall in Hepatic Venous Pressure Gradient (HVPG) by different drugs

Drug	Fall in HVPG	Range	P Value	95% confidence interval
Prapranolol	4.3 ± 1.4	2-6	<0.001	3.1 – 5.4
Carvedilol	4.4 ± 1.8	2-8	<0.001	2.8-5.9
Nitrates	2.8 ± 1.4	2-6	<0.001	1.6-3.9
Propranolol+Nitrate	5.3 ± 1.0	4-7	<0.0001	4.4-6.1
Carved + Nitrate	5.5 ± 1.2	4-7	<0.0001	4.5 – 6.5

The comparative effect of different drug regimens on HVPG is shown in Figure I.

Comparative Effect of Different Drug Regimens on HVPG

Propranolol

Carvedilol

Isosorbide Dinitrate

Propranolol + Isosorbide Dinitrate

Carvedilol + Isosorbide Dinitrate

Figure I:

DISCUSSION

The combination of carvedilol and nitrate has been first time used in our study for the treatment of PHT. In our study, propranolol, carvedilol, propranolol plus isosorbide dinitrate “carvedilol plus isosorbide-dinitrate” caused uniformly good results (drop in HVPg of >20%). However, Isosorbide dinitrate alone, caused a significant decrease in HVPg which was less than cut off value of 20% to call a drug effective. Lebrec et al² and Hillon et al¹³; demonstrated uniformly excellent results of beta-blockers in reducing the Portal Venous Pressure (PVP) in patients of cirrhosis.

Propranolol caused 27% reduction in HVPg in our patients; mean HVPg fall 4.3 ± 1.4 , $P < 0.0001$. Vorobioff J et al, in 1987.¹⁴ studied the effect of acute and chronic administration of propranolol on portal venous pressure in unselected patients of cirrhosis. They found that 60 minutes after acute administration of propranolol, the mean HVPg dropped from 21.7 ± 1.7 to 17.2 ± 5.5 mmHg; % change -17.6 and $p < 0.01$. Bosch J et al¹⁵ assessed the effects of propranolol on azygous venous blood flow and hepatic and systemic hemodynamics in cirrhosis. They found that propranolol at doses achieving effective B-blockade (83 ± 5 mgm) reduced the HVPg from 18.1 ± 0.8 mmHg to 15.9 ± 0.7 mmHg after ($p < 0.001$). Similar results were seen in previous studies by Lebrec et al², Mastai R. et al¹⁶, Groszmann RJ et al.¹⁷

Carvedilol is a relatively new drug to have been used for the treatment of portal hypertension. In our patients, a 25 mg oral dose of carvedilol caused an excellent response (drop in HVPg of 4.4 ± 1.8 mmHg i.e, a drop of 30%. When compared to propranolol, the response to carvedilol was better (30% vs 27%), although the difference did not reach statistical significance ($p = 1$). Rafael B, et al¹² reported that carvedilol markedly reduced HVPg (from 19.5 ± 1.3 to 15.4 ± 1 mmHg $p < 0.001$) and that the HVPg reduction was greater than after propranolol (-20.4 ± 2 vs $-12.7 \pm 2\%$, $p < 0.05$). They suggested that the greater HVPg decrease by Carvedilol is because of reduced hepatic and portocollateral resistance. Han-Chie-Lin et al,¹¹ demonstrated that carvedilol alone is superior to combination of propranolol and isosorbide -5-Mononitrate in reducing HVPg in patients with viral cirrhosis (Carvedilol $18.6 \pm 3.6\%$ drops vs $-10.1 \pm 3.5\%$ drop, $p < 0.05$).

Beta blockers have been used alongwith nitrates in the treatment of PHT to improve the response rate and decrease

the side effects of higher doses of beta-blockers. The combination of propranolol and iso-sorbide -5-mononitrate has been recommended as the first line therapy for prophylaxis of variceal bleeding. The combination of beta blockers and nitrates has yielded synergistic effects. However, so far the combination of carvedilol with nitrate has not been reported. We studied the effects of carvedilol and Isosorbide-dinitrate combination in our study and compared it to carvedilol alone and to propranolol isosorbide dinitrate combination. Carvedilol plus isosorbide dinitrate reduced the HVPg to a greater extent than by carvedilol alone (5.5 ± 1.2 vs 4.4 ± 1.8 mmHg) ($p = 0.10$). Similarly, association of carvedilol with isosorbide dinitrate proved to be better than propranolol alone (5.5 ± 1.2 vs 4.3 ± 1.4 mmHg; $p = 0.40$). The magnitude of fall by Carvedilol + isosorbide dinitrate was -36% vs carvedilol 30% and propranolol-27%.

Isosorbide dinitrate yielded the lowest decrease in HVPg (17.5%)- Mean drop 2.8 ± 1.4 mmHg range 2-6, $p < 0.001$. There are varying reports about the efficacy of nitrates in diminishing HVPg in literature. Some studies have shown that isosorbide-5-mononitrate alone significantly decreased portal pressure in patients with cirrhosis¹⁸, yet other studies¹⁹ showed a lack of effect of isosorbide-mononitrate in the reduction of portal pressure. The beneficial effect of isosorbide-5-mononitrate administration in cirrhotic patients reported from western countries was mostly in alcohol-related disease. It is possible that the different disease entities and races may contribute to the different hemodynamic effects of isosorbide dinitrate in Kashmiri patients with non-alcoholic cirrhosis.

In conclusion, our study demonstrates that propranolol, carvedilol, isosorbide dinitrate, propranolol plus isosorbide dinitrate and carvedilol plus isosorbide dinitrate produce a uniformly good result in decreasing HVPg in patients of non-alcoholic cirrhosis. Besides, it shows that carvedilol is slightly, though not significantly, better than propranolol and when combined with nitrates, it may be the best option for treatment of portal hypertension. These results need further confirmation by carrying out larger studies and possibly by long term follow up of patients on chronic administration of these agents with periodic reassessment of HVPg at 3-monthly or 6-monthly intervals.

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