COMPARISON OF CARVEDILOL VERSUS PROPRANOLOL FOR PREVENTION OF ESOPHAGEAL VARICEAL BLEED IN CIRRHOTIC PATIENTS

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ABSTRACT

Objective: To compare the efficacy of carvedilol versus propranolol for prevention of bleed in esophageal varices in cirrhotic patients.

Material and Methods: Randomized controlled trial was conducted at Medicine Department Post Graduate Medical Institute, Lady Reading Hospital, Peshawar from August 2012 to August 2013. Sample size was taken as 176. Patients were randomized in two groups by opaque sealed envelope method after fulfilling Inclusion Criteria. Patients in group "A" were given Carvedilol (6.25 mg/day) while patients in group "B" were given propranolol (20 mg twice daily). All patients were followed up till the end of 3rd month to determine the efficacy of the drug. Drug was considered effective if there was no variceal bleed till 3 months follow up after start of the drug. Chi square test was applied and P-value of ≤ 0.05 was considered as significant.

Results: Of 176 patients, 88 were in group A and 88 were in group B. One hundred and six (60.2%) were male and 70 (39.8%) were females. Mean age of the whole sample was 49.68 years $\pm$ 7.912 SD, with age range from 35 to 60 years. In carvedilol group the drug was effective in 75/88 patients (85.2%) and the proportion of variceal bleed was 14.8 % (13 patients). In propranolol group, the drug was effective in 64/88 patients (72.7%). The efficacy of carvedilol therapy (success rate 85.2%) in term of preventing the variceal bleeding was greater than propranolol therapy (success rate 72.7%) and this difference in efficacy was statically significant with p-value <0.042.

Conclusion: Carvedilol is significantly more effective than propranolol in the prevention of variceal bleeding in cirrhotic patients with esophageal varices.

Key Words: Chronic Liver Disease, Carvedilol, Variceal bleed, Prophylaxis, propranolol.

INTRODUCTION

Liver cirrhosis is a worldwide problem found in all social layers, races, age groups and both genders.[1] It is the 10th leading cause of death in United States.[2] It is also a common cause of death in Pakistan and frequent cause of admission in our hospitals.[3] Chronic liver disease is the common cause of morbidity and mortality in our community. This increase in morbidity and mortality is due to various complications.[4] Among these complications esophageal variceal bleed is the most serious but preventable one.[5] Its mortality within 6 weeks is in the order of 11-20%. Esophageal varices are present in 40%-60% of cirrhotic patients.[6] These develop at a rate of 5-10% per year and about 25-30% will bleed which is associated with a very poor outcome causing death at a rate of 40% at 6 weeks and 70% at 1 year.[7,8] Primary prophylaxis is therefore considered mandatory in patients with cirrhosis and esophageal varices. Esophageal variceal bleeding occurs only when there is a clinically significant portal hypertension, defined as hepatic vein pressure gradient (HVPG) >12 mmHg.[9-10]

In order to prevent esophageal variceal bleed, various therapeutic modalities are used which include beta-blockers and endoscopic banding.[11] Compared to banding, beta blockers are cheap, easy to administer and noninvasive.[12] Portal pressure depends on blood inflow and on resistance in the portal system. Therefore portal pressure can be lowered by either reducing portal blood flow using splanchnic vasoconstrictors (Non-selective β-blockers), or reducing resistance in the portal system by using vasodilators. Among beta-blockers, propranolol which is a non selective beta blocker is

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most commonly used. It has demonstrated reduction in risk of esophageal variceal bleed from 30% to 14% when compared to placebo.[13] Blockade of β2 receptors located in the splanchnic (mesenteric) vascular bed results in vasoconstriction and reduction in portal blood inflow. That is why non-selective beta-blockers are the recommended first-line therapy for the primary prophylaxis of variceal hemorrhage in cirrhotic patients with varices at high risk for bleeding.[14]

The intrahepatic vascular resistance is another factor for the development of portal hypertension and then leading to esophageal varices and subsequent bleeding in cirrhotic. It is estimated that up to 40% of this intrahepatic vascular resistance is functionally reversible.[15] It pharmacologically represents another major site to modulate portal hypertension. This intra hepatic vascular resistance can be decreased by blocking both alpha-1 and beta receptors.[16] Such a therapeutic agent is carvedilol.[16] Carvedilol is a non-selective beta-blocker that combines both vasodilator and vasoconstrictor effects, with intrinsic alpha-one adrenergic activity, whose haemodynamic effects mimic those of the combination therapy with beta-blocker plus prazosin. In one international study, carvedilol has demonstrated 10% vs. 23% bleed from varices when compared to endoscopic band ligation.[17] A randomized controlled trial has compared propranolol with endoscopic band ligation with bleed rates of 22% vs. 24% respectively in cirrhotic patients.[18] Another randomized controlled prospective study has shown lower rates of esophageal variceal bleed by endoscopic band ligation 5.1% vs. 25% when compared to propranolol.[19] Due to its unique mechanism of action carvedilol is considered an ideal therapy for the prevention of variceal bleeding. It is two to four times more potent than propranolol as a β-receptor blocking drug.[20-21-22] The current study also evaluated the role of carvedilol in patients with varices and to answer the question whether it was more effective than propranolol.

As there is scarcity of international and local published literatures in comparing these two drugs side by side in the prevention of bleed from varices in cirrhotic patients, the aim of this study is to compare the clinical efficacy of carvedilol versus propranolol for the prevention of esophageal variceal bleed in cirrhotic patients in our local population. Propranolol which has shown lesser or equivocal efficacy to endoscopic banding has been in use since long. Comparing these two drugs will enable us whether any change in drug therapy can bring any revolution while dealing with esophageal varices. It will also provide a baseline work for further research on this issue.

MATERIAL AND METHODS

This randomized controlled trial was conducted in the Department of Medicine, Post Graduate Medical Institute, Lady Reading Hospital, Peshawar from August 2012 to August 2013. Sample size was 88 patients in each group, using 10% proportion of variceal bleed in carvedilol[17], 24% in propranolol[18], 95% confidence level and 80% margin of error under WHO software for sample size determination. Sampling technique was non-probability consecutive sampling. Esophageal varices were diagnosed on endoscopy which is the gold standard test and varices were classified as small (<5mm minimally elevated vein above esophageal mucosal surface), medium(tortuous vein occupying less than 1/3 of esophageal lumen) and large(>5mm, occupying more than 1/3 of esophageal lumen). All cirrhotic patients who had proven esophageal varices on endoscopy with age range 18-60 years regardless of gender were included in the study, while patients already receiving beta-blockers or nitrates for prophylaxis of variceal bleed, presence of malignancy, presence of obstructive airway disease, presence of bleeding varices, high grade varices or varices with red wale marks and patients with history of bleeding disorders were excluded. Patients with high grade varices and/or varices with red wale marks were immediately considered for prophylactic banding and therefore were not included in the study.

The study was conducted after approval from hospital ethical committee. Patients were admitted in the medical wards via OPD and emergency department. Patients meeting the inclusion criteria were enrolled in the study after informed written consent. Detailed history and physical examination was undertaken. All patients underwent upper gastrointestinal endoscopy for the presence of esophageal varices.

Patients were randomly allocated in two groups by opaque sealed envelope method. Patients in group "A" were given carvedilol (6.25mg/day) while patients in group "B" were given propranolol (20mg twice daily). They were discharged from the hospital after being taught how to use the drugs. They were also educated about variceal bleed as appearance of frank blood in vomitus or blackish discoloration of stool. All patients were followed up till the end of 3rd month from the start of therapy and repeat endoscopy was done to confirm bleed from esophageal varices to determine the efficacy of the drug. All the baseline and follow up endoscopic examinations were done by single experienced gastroenterologist.

All the above mentioned information including name, age, gender and address were recorded in a pre designed proforma. Strict exclusion criteria were

followed to control confounders and bias in the study results. Data were analyzed by statistical package for social sciences SPSS version 15. Numerical variables like age were presented as Mean ± standard deviation. Categorical variables like gender and efficacy were presented as frequencies and percentages. Chi square test was used to compare the efficacy in two groups (carvedilol vs. propranolol). P-value of ≤0.05 was considered as significant. Efficacy in both groups was also stratified among age and gender to see the effect modifiers. All results were presented in the form of tables.

RESULTS

Various characteristics of patients included in the study are illustrated in the Table 1 and 2. The cause of portal hypertension was liver cirrhosis. The most common cause of liver cirrhosis was chronic viral hepatitis. Chronic hepatitis B, chronic hepatitis C and both chronic hepatitis B and C were found as cause in 67, 87 and 5 patients respectively. In 17 patients the cause of liver cirrhosis was non B and C hepatitis.

Out of 176 study participants the pharmacotherapy was effective in the prevention of variceal bleeding in 139 patients (Success rate 79.0%). The proportion of variceal bleed in whole sample was 21.0% (37 patients). In group A (carvedilol group) the drug was effective in preventing the variceal bleeding in 75/88 patients (85.2%) and the proportion of variceal bleed was 14.8% (13 patients). In group B (propranolol group) the drug was effective in 64/88 patients (72.7%) while variceal bleeding was observed in 24 patients (27.3%). To compare the effectiveness of the conventional (propranolol) and experimental (carvedilol) therapy in the two groups, chi-square was applied. The efficacy of carvedilol therapy (success rate 85.2%) in term of preventing the variceal bleeding was greater than propranolol therapy (success rate 72.7%) and this difference in efficacy was significant with p-value <0.042 (Table 3). The effectiveness of the conventional and experimental therapy in both groups was also stratified among age, gender and to see the effect modifications. Gender-wise the proportion of variceal bleed was more in males (25.5%) than females (14.3%) but this difference was statistically not significant with p-value of 0.075 (Table 3).

When the effectiveness of therapy was stratified against different age groups, the drugs were more effective in younger age groups than older patients and the proportion of variceal haemorrhage was observed more in older patients as compared to younger patients, this difference was statistically significant with p-vale of less than 0.05 (Table 4). Thus the results of this study showed that in patients of liver cirrhosis with esophageal varices, carvedilol is significantly more effective than propranolol for the prevention of variceal bleed (p- value 0.042).

Table 1: Gender wise distribution of patients in two groups

Gender	Group A	Group B	Total
Male	57 (53.8%)	49 (46.2%)	106 (100%)
Female	31 (44.3%)	39 (55.7%)	70 (100%)
Total	88 (100%)	88 (100%)	176

DISCUSSION

The results of this study showed that long-term administration of carvedilol significantly reduces variceal bleeding when compared to propranolol by reducing the portal pressure in cirrhotic patients with esophageal varices. In our study carvedilol was more significantly effective in preventing the variceal bleeding (response rate 85.2%) and the proportion of variceal bleed was only 14.8%. While in propranolol group the response rate was 72.7% and variceal bleeding was observed in 24 patients (27.3%) (P-value 0.042).

Table 2: Age wise distribution of patients in two groups

Group	Gender	Maximum age	Minimum age	Mean age	Std. Deviation
Group A	Male	60	39	49.46	7.268
	Female	58	41	49.03	7.250
	Both Gender	60	39	49.31	7.223
Group B	Male	60	36	52.47	8.500
	Female	56	35	47.03	7.744
	Both Gender	60	35	50.06	8.371
Total	Male	60	36	50.85	7.968
	Female	58	35	47.91	7.543
	Both Gender	60	35	49.68	7.912

Table 3: Subgroup analysis of effectiveness of the therapy in two groups according to the gender

Gender			Group		Total	P-value
			Group A	Group B	Group A & B	0.260
Male	Effectiveness	Yes	45	34	79	
			78.9%	69.4%	74.5%	
			12	15	27	
			21.1%	30.6%	25.5%	
	Total		57	49	106	
			100.0%	100.0%	100.0%	
Female	Effectiveness	Yes	30	30	60	0.032
			96.8%	79.5%	87.1%	
		No	1	9	10	
			3.2%	20.5%	12.9%	
	Total		31	39	70	
			100.0%	100.0%	100.0%	

Table 4: Subgroup analysis of effectiveness of the therapy in two groups according to the age group

Group	Age group		Effectiveness		Total	P-value
			Yes	No		0.124
Group A	30-40		11 (14.66%)	1 (7.69%)	12 (13.63%)	
	41-50		45 (60.0%)	7 (53.8%)	52 (59.09%)	
	51-60		19 (25.0%)	5 (38.46%)	24 (27.27%)	
	Total		75 (100.0%)	13 (100.0%)	88 (100.0%)	
Group B		30-40	8(11.42%)	0(0.0%)	8(9.09%)	P-value
		41-50	35(50.0%)	5(27.77%)	40(45.45%)	0.5
		51-60	27(38.57%)	13(72.22%)	40(45.45%)	
	Total		70(100.0%)	18(100.0%)	88(100.0%)	

Although to our knowledge there is no local data on this subject, carvedilol has been compared to propranolol in several international clinical trials.[23-5] In most of these studies the criteria for determining the efficacy was a reduction in Hepatic Vein Pressure Gradient (HVPG) at least below 12mmHg. Clinical trials evaluating the acute hemodynamic effects of carvedilol at a dose of 25mg on portal pressure reported a reduction in HVPG by 17-27% from baseline measurements. However in these studies the incidence of systemic hypotension was significantly higher in the carvedilol group.[23-24]

Similarly the hemodynamic effects of chronic administration of carvedilol have been reported in several trials using variable dosages between 12.5 and 50 mg/day.[25-8] Among these trials Banares et al, reported the longest follow-up trial of 12 weeks in 51 cirrhotic patients (26/carvidelol, 25/propranolol).[26] The carvedilol doses were administrated at 12.5-50mg (mean 31 ± 4 mg/d) starting at 6.25 mg and titrated up every 4 days according to blood pressure and heart rate. Chronic carvedilol administration resulted in 58% hemodynamic response rate compared to 23% response rate in the propranolol group.

Response rates for both drugs are quite lower than our reported success rate for carvedilol and propranolol. This difference in response rate may attributed to several reasons including number and selection criteria for patients, different methodology, differences in the doses of two drugs and determining the success rate in term of reduction in HVPG rather than subtle or over bleeding from esophageal varices as was the criteria of efficacy in our study.

Banares et al used much higher dosages than ours. However higher doses are associated with much more side effects and noncompliance as compared to

lower doses. It is doubtful whether such high doses are required, because it has been demonstrated in two previous studies that a lower fixed dose can result in a similar magnitude of portal pressure reduction with minimal side-effects. Both these trials have also reported the efficacy of carvedilol in term of reduction in HVPG by 23-43% from baseline measurements.

CONCLUSION

The success rate of carvedilol was significantly higher than propranolol in term of prevention of bleeding from esophageal varices. The proportion of bleeding from varices was significantly greater in conventional propranolol group than carvedilol group.

LIMITATION

The findings in our study and the earlier observation that carvedilol appears to have superior portal hypotensive effects to propranolol, suggest that carvedilol should be assessed in large randomized controlled trials for the primary prevention of variceal haemorrhage.

REFERENCES

1. Shafi F, Asad R, Azam M, Aftab M. Frequency of duodenal ulcer in cirrhosis of liver. Pak J Med Health Sci 2010; 4: 56-60.
2. Shah ZH, Sarwar S, Saleem K, Abaidullah S, Mehboob F, Afzal A et al. Identification of non-endoscopic predictors of esophageal varices in cirrhosis. Pak J Med Health Sci 2011; 5: 257-61.
3. Almani SA, Memon AS, MemonAI, Shah I, Rahpoto Q, Solangi R. Cirrhosis of liver: etiological factors, complications and prognosis. J Liaquat Uni Med Health Sci 2008; 7: 61-66.
4. Shaikh SU, Ghani H, Memon S, BalochGH, Jaffery M, Shaikh K. MELD era: is this time to replace the original child-pugh score in patients with decompensated cirrhosis of liver. J Coll Physicians Surg Pak 2010; 20: 432-35.
5. Wang MT, Liu T, Ma XQ, He J. Prognostic factors associated with rebleeding in cirrhotic inpatients complicated with esophageal variceal bleeding. Chin Med J (Engl) 2011; 124: 1493-97.
6. Lee CH. Prevention of esophageal variceal bleeding. Korean J Gastroenterol 2010; 56: 155-67.
7. Zhang C, Thabut D, Kamath PS, Shah VH. Esophageal varices in cirrhotic patients: from variceal screening to primary prophylaxis of the first esophagealvariceal bleeding. Liver Int2011; 31: 108-19.
8. Sharma P, Sarin SK. Improved survival with the patients with variceal bleed. Int J Hepatol 2011; 2011: 35: 6919.
9. Armonis A, Patch D & Burroughs AK. Hepatic venous pressure measurement: an old test as new prognostic marker in cirrhosis? Hepatology 1997; 25: 245-48.
10. Merkel C & Gatta A. Can we predict the first variceal bleeding in the individual patient with cirrhosis and esophageal varices. J Hepatol 1991; 13: 378.
11. Triantos CK, Burroughs AK. Prevention of the development of varices and first portal hypertensive bleeding episode. Best Pract Res Clin Gastroenterol 2007; 21: 31-42.
12. Abraldes JG, Bosch J. The treatment of acute variceal bleeding. J Clin Gastroenterol 2007; 41: 12-17.
13. Longacre AV, Imaeda A, Garcia-Tsao G, Fraenkel LA. Pilot project examining the predicted preferences of patients and physicians in the primary prophylaxis of variceal hemorrhage. Hepatol 2008; 47: 169-76.
14. deFranchis R. Evolving Consensus in Portal Hypertension Report of the Baveno IV Consensus Workshop on methodology of diagnosis and therapy in portal hypertension. J Hepatol 2005; 43: 167-76.
15. Bathal PS, Grossmann HJ. Reduction of the increased portal vascular resistance of the isolated perfused cirrhotic rat liver by vasodilators. J Hepatol. 1985; 1: 325-29.
16. Tripathi D, Hayes PC. The role of carvedilol in the management of portal hypertension. Eur J Gastroenterol Hepatol 2010; 22: 905-11.
17. Tripathi D, Ferguson JW, Kochar N, Leithead JA, Therapondos G, McAvoy NC et al. Randomized controlled trial of carvedilol versus variceal band ligation for the prevention of the first variceal bleed. Hepatology 2009; 50: 825-33.
18. Lay CS, Tsai YT, Lee FY, Lai YL, Yu CJ, Chen CB et al. Endoscopic variceal ligation versus propranolol in prophylaxis of first variceal bleeding in patients with cirrhosis. J Gastroenterol Hepatol 2006; 21: 413-19.
19. Pérez-Ayuso RM, Valderrama S, Espinoza M, Rollán A, Sánchez R, Otarola F et al. Endoscopic band ligation versus propranolol for the primary prophylaxis of variceal bleeding in cirrhotic patients with high risk esophageal varices. Ann Hepatol 2010; 9: 15-22.
20. Albillos A, Garcia-Pagan JC, Iborra J et al. Propranolol plus prazosin compared with propranolol plus isosorbide-5-mononitrate in the treatment of portal hypertension. Gastroenterology 1998; 115: 116-23.
21. Al-Shaqha WM, Hamdy A, Alnaim L, editors. Alphabetical listing of drugs. 4th ed. Ohio: Lexi-Comp Inc; 2009. Carvedilol. In; pp. 432-35.
22. Ruffolo RR, Jr, Gellai M, Hiehle JP, Willette RN. The pharmacology of carvedilol. Eur J Clin Pharmacol. 1990; 38: 82-88.

23. Banares R, Moitinho E, Piqueras B, Casado M. Carvedilol, a new nonselective beta-blocker with intrinsic anti- Alpha1- adrenergic activity, has a greater portal hypotensive effect than propranolol in patients with cirrhosis. Hepatology. 1999; 30: 79-83.

24. Forrest EH, Bouchier IA, Hayes PC. Acute haemodynamic changes after oral carvedilol, a vasodilating beta-blocker, in patients with cirrhosis. J Hepatol. 1996; 25: 909-15.

25. De BK, Das D, Sen S, Biswas PK. Acute and 7-day portal pressure response to carvedilol and propranolol in cirrhotics. J Gastroenterol Hepatol. 2002; 17: 183-89.

26. Banares R, Moitinho E, Matilla A, Garcia-Pagan JC. Randomized comparison of long-term carvedilol and propranolol administration in the treatment of portal hypertension in cirrhosis. Hepatology. 2002; 36: 1367-73.

AUTHOR'S CONTRIBUTION

Following authors have made substantial contributions to the manuscript as under:

Khan AM: Data collection and typing.

Ziauddin: Bibliography and statistics.

Ali G: Idea and operating surgeon.

Authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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