Original Article

Carvedilol vs endoscopic band ligation: primary prophylaxis of variceal bleed

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Objective: To compare variceal bleed in patients of liver cirrhosis receiving carvedilol versus esophageal band ligation as primary prophylaxis within three months of treatment.

Methodology: This randomized controlled trial was carried out at Department of Medicine, District Head Quarter Hospital, Rawalpindi from September 1st 2016 to February 28th 2017 with 254 patients of cirrhosis with esophageal varices. They were divided into 2 groups with 127 each: Carvedilol group and endoscopic band ligation. Data were recorded at baseline and at regular follow ups for three months or first variceal bleed. Data analysis was performed with SPSS 20. Effect modifiers and confounders were controlled through stratification and Chi Square test applied with $p \leq 0.05$ significant.

Results: Out of 254 patients, 188 (74.0%) were male and 66 (26.0%) females. Mean age was 55.60 ± 9.01 years. Mean Child Pugh Score was 6.59 ± 4.09. Frequency of variceal bleeding in patients receiving carvedilol was 35 (27.6%) compared to 27 (21.3%) of esophageal band ligation as primary prophylaxis within three months of treatment.

Conclusion: Variceal bleeding in liver cirrhosis patients taking carvedilol had no significant difference as opposed to esophageal band ligation and both regimens can be used for primary prophylaxis. Carvedilol is helpful in reduction of unnecessary endoscopy related expenditure and discomfort.

Keywords: Carvedilol, endoscopic band ligation, cirrhosis, esophageal varies.

INTRODUCTION

Variceal hemorrhage is a serious complication of portal hypertension, especially in patients of cirrhosis. Liver cirrhosis is major public health problem worldwide.[1] At diagnosis, up to 70% patients with decompensated cirrhosis have esophageal varices and almost 30% will have variceal bleed in the first year.[2] Esophageal varices makes up almost 10% cases of upper gastrointestinal bleeding in developed world and 15% mortality.[3]

There are mainly two options available for the prevention of variceal bleed, pharmacological versus endoscopic therapy. Non-selective beta-blockers including nadolol and propranolol have been used for almost 30 years for prophylaxis.[4] Recently, non-cardioselective beta-blockers such as carvedilol have been tried in prophylaxis with mild inherent anti-α-1-adrenergic activity reducing portal hypertension, porto-collateral resistance and hepatic stellate cells intrahepatic resistance.[5]

Endoscopic band ligation (EBL) is the preferred approach if endoscopic intervention is sought. However, the recurrence rate and cost is quite high as the procedure needs to be repeated up to 7 times for complete obliteration of varices.[6] Studies have shown no benefit of EBL over beta-blockers for bleed prophylaxis.[7,8] In a randomized trial with 152 patients by Tripathi et al carvedilol had lower rates of first variceal haemorrhage compared with EBL (10% vs 23%).[9] Shah et al, reported carvedilol had comparable bleeding risk to band ligation (8.5% vs 6.9%).[10] Variceal bleeding occurred in 36.4% and 35.5% cases among the carvedilol and EBL group, respectively in a study by Stanley et al.[11] The objective of this study was to compare variceal bleed in patients of liver cirrhosis receiving carvedilol versus EBL as primary prophylaxis within three months of treatment.

METHODOLOGY

After approval from R&E Committee Rawalpindi Medical College and Allied Hospitals Rawalpindi dated 8th October 2015, this randomized controlled trail was conducted at Department of Medicine, District Head Quarter Hospital, Rawalpindi from September 2016 to February 2017. A sample size of 254 patients (127 in each group using lottery method) keeping power of test 80% and confidence interval of 95% (expected percentage 23% Vs 10%) was calculated.[6]

Using non-probability consecutive sampling technique and after taking informed consent, 254 patients aged 18 – 75 years of both gender with cirrhosis and

esophageal varices were enrolled. Patient with previous history of variceal bleeding or undergone EBL, allergy to carvedilol, history of obstructive airway disease, and those already on beta blocker therapy were excluded from the study.

Patients in carvedilol group were started on dose of once daily 6.25mg initially for 1 week and subsequently titrated to twice daily 6.25mg. In EBL group, Saeed Six Shooter Multi-Band Ligator® connected to a video endoscope (Olympus, Tokyo, Japan) was used and the procedure was done after 3 weeks repeatedly until achievement of variceal obliteration. Patients in both groups were followed up for up to duration of three months or first variceal bleed, whichever was earlier.

Cirrhosis was defined as coarse liver echo texture on ultrasound, and grading was done by Child Pugh score (Table 1). Esophageal varices were classified by Westaby Classification (Table 2). Variceal bleed was defined as overt clinical hematemesis or melena and hemoglobin drop >2g/dl within 24 hrs of hospital admission.

Statistical Analysis: Data were analysed using SPSS version 20. Effect modifiers and confounders such as age, gender, duration of disease were controlled through stratification and Chi Square test applied by taking p-value ≤ 0.05 significant.

RESULTS

Total 254 patients enrolled in the study were divided into two groups with 127 patients each. Mean age of the patients was 55.60 ± 9.01 years (range 18 – 75). Mean disease duration was 7.12 ± 2.57 months with 188 (74.0%) male and 66 (26.0%) females. Mean Child Pugh Score was 6.59 ± 4.09. In the carvedilol group, mean age of the patients was 55.68 ± 9.60 years, mean disease duration was 7.04 ± 2.33 months with 92 (72.4%) male and 35 (27.6%) females. Mean Child Pugh Score

Table 1: Child-Pugh Classification.

Clinical and Lab Criteria	Points		
	1	**2**	**3**
Encephalopathy	None	Grade I/II	Grade III/IV
Ascites	None	Mild to moderate	Severe
Bilirubin (mg/dl)	< 2	2 – 3	> 3
Albumin (g/dl)	> 3.5	2.8 – 3.5	< 2.8
PT (sec)	< 4	4 – 6	> 6
Interpretation: After adding points for each parameter (total score), Class A: 5 to 6 points (least severe liver disease), Class B: 7 to 9 points (moderately severe liver disease), Class C: 10 to 15 points (most severe liver disease)			

Table 2: Westaby Classification of esophageal varices.

Grade	Endoscopic appearance
Grade 1	Varices appearing as slight protrusion above mucosa, which can be depressed with insufflations.
Grade 2	Varices occupying < 50% of the lumen.
Grade 3	Varices occupying > 50% of the lumen and which are very close to each other with confluent appearance.

Table 3: Comparison of demographic information and variceal bleed of both groups.

Demographic Variable	Variceal Bleed	Group Assigned	
		Carvedilol	**EBL**
Age group:			
18 – 40 years	Yes	1 (11.1%)	2 (22.2%)
	No	8 (88.9%)	7 (77.8%)
40 – 75 years	Yes	26 (22.0%)	33 (28.0%)
	No	92 (78.0%)	85 (72.0%)
Gender			
Male	Yes	16 (17.4%)	24 (25.0%)
	No	76 (82.6%)	72 (75.0%)
Female	Yes	11 (31.4%)	11 (35.5%)
	No	24 (68.6%)	20 (65.5%)
Duration of disease			
< 12 months	Yes	18 (15.7%)	23 (20.5%)
	No	97 (84.3%)	89 (79.5%)
> 12 months	Yes	9 (75.0%)	12 (80.0%)
	No	3 (25.0%)	3 (20.0%)

was 6.75 ± 5.55. In EBL group, mean age of the patients was 55.52 ± 8.42 years, mean disease duration was 7.20 ± 2.80 months with 96 (75.6%) male and 31 (24.4%) females. Mean Child Pugh Score was 6.43 ± 1.65.

On follow up, variceal bleeding was seen in 62 (24.4%) of the patients. Variceal bleed developed in 35 (27.6%) patients in carvedilol group and in 27 (21.3%) in band ligation group (Table 3). No statistical significant association of variceal bleed was seen with age (1.107, (1, 254), p = .293), gender (1.624, (1, 254), p = .203) and duration of disease (.914, (1, 254), p = .339).

DISCUSSION

Cirrhosis of the liver is responsible for up to 90% cases of portal hypertension[1] leading to formation of porto-systemic collaterals, which triggers development of gastric and esophageal varices. At time of diagnosis, approximately 30% patients of compensated cirrhosis and 70% of decompensated cirrhosis have varices.[2] Bleeding risk at one-year is 5 – 15%, depending upon size of varices and almost half the patients die after variceal bleed despite therapy.[8] In a study by Cordon et al,[12] the presence of esophageal varices varied from 8 – 83% at 10 years of follow up.

The risk of a cirrhotic patient developing esophageal varices varies greatly, however disease duration may play a role. The mean age of the patients in our study was 55.60 ± 9.01 years with range from 18 to 75 years, the mean duration of disease was 7.12 ± 2.57 months with 188 (74.0%) male and 66 (26.0%) females, which is comparable to other studies.[9,10] In our study, variceal bleeding was seen in 62 (24.4%) of the patients and the frequency of variceal bleed was 35 (27.6%) in carvedilol group and 27 (21.3%) in band ligation group. This is comparable to Tripathi et al.[9] (10% vs 23%) and Stanley et al.[11] (36.4% vs 35.5%).

However, Shah et al[10] reported lower rates with both carvedilol and band ligation but both were comparable (8.5% vs 6.9%). As carvedilol is taken orally, it helps in significant reduction of endoscopy related expenditure and discomfort. Accounting for its ease of administration, low cost and reduction of procedure-related mortality in our population, beta-blockers maybe recommended as first-line treatment for the primary prophylaxis of esophageal variceal bleeding.

It should not be forgotten that 30% cirrhotic patients with bleed may be due to other causes such as peptic ulcer, antral erosions, gastropathy or varicose veins of gastric fundus.[12] Sclerotherapy and rubber band ligation are currently the most commonly used endoscopic methods for variceal bleed control.[12] However, the most efficient procedure for controlling acute bleeding remains under debate. A meta-analysis[13] reported that all-cause rebleeding was lower using combination of drug and endoscopic therapy as compared to either therapy alone, with no difference in mortality. In another meta-analysis,[14] the addition of endoscopic therapy with beta-blockers vastly reduced rebleeding risk and increased survival as opposed to endoscopic therapy alone.

Thus, current guidelines suggest the concomitant use of beta-blockers and endoscopic therapy in preventing variceal hemorrhage. In cases when endoscopic ligation cannot be done, combining nitrates with beta-blockers would help in portal hypertension reduction.[15] In patients with beta-blockers contraindication or intolerance, periodical band ligation should be employed.[14] Transhepatic intrajugular portosystemic shunt (TIPS) with polytetrafluoroethylene should be considered in patients who fail pharmacological and endoscopic therapy[16] and surgical shunting (Child-Pugh A and B) is an alternate to TIPS unavailability. Liver transplantation provides efficient long-term improvement in suitable candidates and must be offered[17] with TIPS as a time-sparing intervention until transplantation.

CONCLUSION

We conclude that variceal bleeding in liver cirrhosis patients taking carvedilol had no significant difference as opposed to esophageal band ligation and both regimens can be used as a substitute. However, carvedilol is helpful in reduction of unnecessary endoscopy related expenditure and patient discomfort.

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