Original article

Comparison of carvedilol and propranolol for secondary prophylaxis of variceal bleed in cirrhotic patients

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ABSTRACT

Background: Portal hypertension is predominant sequelae of liver cirrhosis. Carvedilol and propranolol are used to decrease portal pressure which in turn prevents reoccurrence of bleeding episodes in cirrhotic patients diagnosed and treated for upper gastrointestinal bleeding. Only scarce data is available regarding effectiveness of carvedilol and propranolol as prophylaxis. The aim of this study was to compare the effectiveness of carvedilol and propranolol to prevent reoccurrence of bleeding in cirrhotic patients.

Patients and Methods: This quasi experimental study was conducted at the Department of Gastroenterology, Shaikh Zayed Hospital, Lahore, Pakistan from November 2016 to October 2017. Patients suffering from chronic liver disease and had first experience of bleed due to esophageal varices identified and treated on the upper gastrointestinal (GI) endoscopy were included in the study. Demography and Child-Turcotte-Pugh (CTP) class were recorded. In order to prevent reoccurrence of bleeding, these patients were randomly allocated prophylaxis treatment groups comprising 75 patients each; Group A (carvedilol 6.25 mg BD) and Group B (propranolol 20mg TDS) for 6 months. Assessment for bleeding episode (if any) and decrease in hemodynamical parameters like pulse rate (PR), mean arterial pressure (MAP) and portal vein flow (PVF) were assessed after 3 and six months intervals. Drug A or B was considered effective if there was no clinical evidence of re-bleed (melena/hematemesis and drop in hemoglobin levels) and decrease in hemodynamical parameters were observed. Data was entered and analyzed using SPSS version 20.0.

Results: Out of 75 patients in each group, 45 (60%) were male in group A and 48 (64%) were male in group B. There was no significant difference in terms of gender, age and CTP class in both groups. Recurrence of upper GI bleeding was seen in 15 (25.3%) patients in group A as compared to 32 (42.66%) in group B ($p < 0.05$). Significant reduction in mean arterial pressure (MAP), heart rate and portal vein flow (PVF) was observed in group A at both 3 and 6 months (p-value< 0.05).

Conclusion: Carvedilol when compared to propranolol is better in all parameters measured in this study to reduce portal pressure and decrease bleeding episodes.

Keywords:
Variceal bleed, propranolol, carvedilol, MAP, PVF.

INTRODUCTION

Liver cirrhosis is one of the leading causes of morbidity and mortality in the world.[1,2] Common causes includes viral hepatitis, including B and C, alcoholic liver disease and metabolic diseases. Liver cirrhosis can lead to portal hypertension which is defined as portal pressure gradient of >5mmHg (difference of pressure between wedged and free hepatic vein).[3-5] Varices develop when portal pressure reaches up to 10 mmHg and bleeding occurs at a pressure of >12mmHg.[6] Variceal hemorrhage is associated with 10-20% mortality at 6 weeks.[7] For primary prophylaxis, beta blockers like nadolol, propranolol and carvedilol are used or alternatively endoscopic band ligation is performed.[7] For secondary prophylaxis, β-blockers along with endoscopic obliteration of varices are the recommended line of action.[7,8] Propranolol is a non-selective β-blocker (NSBB) and Carvedilol is also a NSBB with a mild anti-α1 adrenergic activity.[8] Various studies have compared the effectiveness of propranolol and carvedilol in secondary prophylaxis of variceal bleeding.[9,10] A 20% reduction of portal pressure is considered adequate to reduce the risk of variceal hemorrhage. Hepatic venous pressure gradient (HVPG) is used to measure portal pressure and is considered best investigation modality but it is invasive, costly and needs expertise which is not widely available.[11] In limited resource countries, like Pakistan indirect markers of portal pressure reduction like heart rate, mean arterial pressure, portal vein flow and number of bleeding episodes while on drugs can be used for assessment of response. In this study, comparison in reduction in heart rate, mean arterial pressure, portal vein flow and recurrence of bleeding episodes on propranolol and carvedilol was done in cirrhotic patients who had an initial episode of bleeding. Monitoring of the response is assessed by reduction in number of Gl bleeding episodes. It is important to have such data so that evidence-based practice can be implemented.

Competing interest: The authors have declared no competing interests exist.
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PATIENTS AND METHODS

The study was conducted at Department of Gastroenterology, Shaikh Zayed Hospital, Lahore, from November 2016 to October 2017. After taking informed consents, 150 cirrhotic patients of both genders between the ages of 18 to 65 years, presented to GI department with complaints of upper GI bleeding were selected. All cirrhotic patients presenting with first episode of upper GI bleeding, whom esophagogastroduodenoscopy (EGD) confirmed varices as cause of bleeding were included. Patients with hematemesis other than due to esophageal varices diagnosed on upper GI endoscopy and carrying any contraindications to beta blockers or who were already on β-blockers were excluded from the study. Patients were explained the purpose of the study and an informed consent was obtained from all participants. Patients were randomly allocated to group A (carvedilol) and group B (propranolol); each group comprising 75 patients. Demographic details and Child-Turcotte-Pugh CTP class were recorded. All baseline parameters like pulse rate (PR), mean arterial pressure (MAP), and hemoglobin levels were documented. For the estimation of baseline portal vein flow (PVF), patients were referred to radiology department to get their Portal Ultrasound. In order to prevent reoccurrence of bleeding, these patients were randomly allocated prophylaxis treatment i.e. group A (carvedilol 6.25 mg BD) and group B (propranolol 20mg TDS) for 6 months. Patients were followed weekly and dose increased if required till target heart rate was achieved until and unless adverse effects prevented from increasing the dose (in this case, maximum tolerated dose was continued). Initially carvedilol was given at 6.25 mg /day at low dose and if no side effects and symptoms observed then it was tittered up to 25 mg/day maximally or till the target heart rate of < 25% from the baseline or 55–60 beats/min achieved. The dose was not titrated up in patients who showed any side effects, like systolic hypotension (blood pressure <90 mm Hg) or bradycardia (heart rate <55 beats per minute). Propranolol 20 mg thrice daily was given in the group B. If patient tolerated the prescribed dose then it was gradually increased up to maximum 160 mg per 24 hours or till the heart rate of <25% from baseline or 55–60 beats/minute target was achieved. EGD was done in each group every 2 weeks till obliteration of varices and drugs (carvedilol and propranolol) were continued afterwards. Assessment for bleeding episode (if any) and decrease in hemodynamical parameters like PR, MAP and PVF were assessed after 3 and six months follow ups. The study end point was noted in the form of re-bleeding episodes in six months period from date of recruitment. Drug A or B was marked as effective if there was no clinical evidence of re-bleed (melena/hematemesis and drop in hemoglobin levels) and decrease in hemodynamic parameters (PR, MAP, PVF) were observed. All data was entered and analyzed using SPSS version 22. The t-test was applied to compare the effectiveness of both carvedilol and propranolol in terms of significant difference with p-values. Significant p-values were considered at <0.05

RESULTS

In this study, there were 75 cases in each group; 45 (60%) were male in group A and 48 (64%) were male in group B. There was no significant difference in terms of gender, age and CPT class in both the groups (Table 1).

Recurrence of upper GI bleeding was seen in 25.3% (15/75) of cases in Group A as compared to 42.6% (32/75) in B and this difference was statistically significant both at 3 and 6 months with p-values of 0.05 and 0.01 respectively. Reduction of MAP and heart rate

Table 1: Characteristics of patients in both groups

Characteristics	Group A N (%)	Group B N (%)	p-value
Male	45 (60%)	48 (64%)	0.95
Female	30 (40%)	27 (36%)	0.93
Age	47.76±9.77	49.81±10.23	0.88
Child Pugh Class A	4 (5.33%)	3 (4%)	067
Child Pugh Class B	22 (29.33%)	25 (33.33%)	0.74
Child Pugh Class C	49 (65.34%)	47 (62.67%)	0.89

Table 2: Comparison of rebleeding and hemodynamic response with carvedilol and propranolol

Recurrence GI bleeding	Carvedilol	Propranolol	p- value
Baseline (0 month)	2 (2.67%)	3 (4%)	0.87
3 months	7 (9.33%)	14 (18.67%)	0.05
6 months	6 (8%)	15 (20%)	0.01
Reduction in MAP (mmHg)			
Baseline (0 month)	- 7.11±0.89	- 6.14±0.45	0.72
3 months	- 10.23±0.98	-5.21±0.52	0.02
6 months	-12.67±1.31	-5.78±0.57	0.01
Heart rate (beats/minute)			
Baseline (0 month)	83±19	82±15	0.91
3 months	76±13	79±14	0.04
6 months	67±9	74±13	0.04
Fall in mean hemoglobin (gm/dL)			
Baseline (0 month)	0.91±0.03	1.21±0.31	0.24

3 months	0.89±0.06	1.18±0.30	0.24
6 months	0.87±0.06	2.21±0.47	0.04
Portal venous flow (ml/min)			
Baseline (0 month)	814.23±123.78	801.56±127.89	0.94
3 months	634.11±97.56	719.45±103.21	0.01
6 months	521.81±76.23	621.33±81.56	0.02

were more in group A at both 3 and 6 months. There was no significant difference in terms of fall in hemoglobin at 3 months while there was significant hemoglobin drop in group B at 6 months follow up where it was 2.21±0.47 as compared to 0.87±0.06 mg/dl with p-value=0.04. PVF was also significantly reduced in carvedilol group both at 3 and 6 months; being 521.81±76.23 ml/min in group A and 621.33±81.56 ml/min in group B at 6 months with p=0.02. There were no significant side effects in both the groups. Table 2 summarizes comparison of various study parameters in each group. Chest tightness was the most common complication complained by 5 (6.67%) patients in each group.

DISCUSSION

Portal hypertension is one the most devastating complications of liver disease.[12] Portal hypertension develops as a result of stiffening of liver parenchyma which results in increased resistance to portal venous flow.[13,14] Propranolol is in use for management of portal hypertension for decades. With the advent of new β-blockers like carvedilol and their promising role and clear benefit over propranolol in cardiac patients, there was a need to see the effectiveness in decreasing the portal pressure by using carvedilol. Therefore, effort made to compare the effectiveness both drugs in reducing variceal bleed episodes in cirrhotic patients as secondary prophylaxis. Although hepatic venous pressure gradient is the best investigation to measure portal pressure but it is invasive, costly and needs certain level of expertise to perform which is not widely available.[11] In clinical setting, heart rate is measured to assess the effectiveness of different drugs prescribed to target portal pressure reduction. Different world societies and guidelines laid down by them also recommend reduction in heart rate to assess the effectiveness of β-blockers to reduce portal pressure[15]. In this study, reduction in MAP, PVF and number of bleeding episodes in addition to heart rate reduction were evaluated as parameters for decrease in portal pressure. Recurrence of GI bleeding was seen in 15 (15.33%) patients treated with carvedilol and 32 (42.66%) treated with propranolol with significant difference in all the follow ups. There were also significantly more drops in hemoglobin with propranolol where it was 2.21±0.47 as compared to 0.87±0.06 mg/dl (p 0.04). This observation is similar to previous reports.[14-16] The findings of the present study were also supported by Aguilar-Olivos and coworkers who reported 79 patients out of 153 patients with alcoholic liver disease and ascites given carvedilol and 74 were treated with drug propranolol. Hepatic venous pressure gradient (HVPG) reduced up to 20% by carvedilol than propranolol in 60% of patients; hence also reducing the recurrence of GI bleeding.[16] Moreover, there is minimal side effects of both drugs reported. This finding was also consistent with another variable studied in the present study where regarding the dynamics of portal circulation, as compared to HVPG, portal venous flow (PVF) was measured and it was also significantly reduced in carvedilol group both at 3 and 6 months.[16] Significant reduction of MAP was observed in group A at all the intervals of assessment. This finding is similar to that reported by Bañares and coauthors that the effectiveness of carvedilol is dose dependent and better.[17] However, some studies have shown that carvedilol even with low dose (12.5 mg/day) caused decrease systemic vasodilation that will decrease the portal hypertension.[18-20] This belief was also strengthened by the findings of two meta-analyses by Razon-Gonzalez and group and Reiberger and colleagues who also studied carvedilol and propranolol in patients with upper GI bleed and found that carvedilol is superior than propranolol in decreasing the mean arterial pressure (MAP) significantly and therefore decreasing the hepatic venous pressure gradient (HVPG).[21,22] Sinagra and coauthors reported patients who were taking propanalol and carvedilol for long period of time showed severe hypotension as a side effect due to its property of decreasing MAP which was also seen in the present study but none of the enrolled patient in this study reported such a drop in blood pressure which required to stop treatment or reduce dose.[23]

In this study, majority of patients were in Child Class C both in groups A (65.34%) and B (62.67%). Previous studies reported that Child Class C is associated with significantly higher number of bleeding episodes.[14,24] Majority of the patients in this study were in class C and they responded better with carvedilol. Carvedilol may be regarded as a better choice in CTP Class C.

CONCLUSION

Carvedilol is significantly better as compared to propranolol in reducing the recurrence of GI bleed, fall in hemoglobin, reduction in MAP, heart rate reduction and in decreasing portal venous flow at 3 and 6 months with minimal side effects.

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