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IMPROVEMENT IN THROMBOCYTOPENIA AFTER CARVEDILOL USE IN HEPATITIS C CIRRHOTIC PATIENTS.

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ABSTRACT: Carvedilol is a β-blocker (non-selective). It causes vasoconstriction in the splanchnic vessels and causes reduction of portal inflow. Hence this change causes less destruction of platelets in the patients having splenomegaly with portal hypertension and cirrhosis. **Objectives:** The objective of the study is to find out the effect of carvedilol on thrombocytopenia in cirrhotic patients of hepatitis C. **Study Design:** Descriptive study. **Settings:** Department of Gastroenterology, Fatima Memorial Hospital, Lahore. **Period:** Six months from 17th October 2015 to 16th April 2016. **Material & Method:** Data was collected using designed proformas. All patients with hepatitis C having cirrhosis of liver, splenomegaly and a platelet count of less than 100,000/mm3 were included after taking informed consent. Dose of carvedilol was managed so that 25% reduction in heart rate was achieved. Platelet count was repeated after two weeks. Blood pressure, pulse and platelet count before and after 25% reduction in heart rate with carvedilol was compared. Changes in platelet count, blood pressure, pulse and dose of carvedilol were also calculated. <0.05 p value was taken as significant. **Results:** A total of 66% patients responded to carvedilol therapy and showedmean rise in platelet count of 16 ± 10.3. (P-Value <0.05). Changes in platelet count with change in blood pressure, pulse and with dose of carvedilol were found to be significant. (P<0.05). **Conclusion:** Carvedilol causes improvement in thrombocytopenia in cirrhotic patients.

Key words: Cirrhotic Patients, Carvedilol, Hepatitis C, Thrombocytopenia.

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INTRODUCTION

Hepatitis C virus (HCV) has the annual frequency of 170 million people worldwide.[1] Almost 80% of the infected patients progress to chronic hepatitis and as much as 30% advance to cirrhosis.[1,2] It is considered that 25% of the HCV infected patients develop hepatocellular carcinoma (HCC).[2,3] In 2002, among 1.4 million deaths associated with chronic liver disease (CLD), more than 280,000 deaths were due to HCV-related liver disease.[4,5] In Pakistan, hepatitis C virus infection is the most common cause of cirrhosis.[6] In Karachi, according to a study, out of 2965 general patients 379(12.8%) were anti-HCV positive.[7] The most serious and worrisome complication of cirrhosis is portal hypertension. As the normal pressure in the portal vein is 5-10 mmHg. In case of portal hypertension the pressure rises to 12mmHg or more due to dilatation of venous channels. Hence it leads to the formation of collaterals with the systemic venous system; the most important site is at the gastro esophageal junction. Here it leads to the development of esophageal and gastric varices. These varices are fragile and can get ruptured leading to life threatening upper gastrointestinal bleeding.[8] It is the hypersplenism due to portal hypertension that leads to thrombocytopenia. This adds to the grave morbidity and mortality of gastrointestinal bleeding.[9]

If it is possible to reduce the portal pressure, the variceal bleedingcan minimize. It in turn reduces the destruction of platelets in the enlarged spleen. Hence if this is required, a medical therapy with beta blockers like propranolol or carvedilol can be helpful.[10] With propranolol there was an increase in platelet count in 62.7% of patients of cirrhosis with portal hypertension.[11] Carvedilol is another

beta blocker, a non-selective one, which causes vasoconstriction of the splanchnic arteries. It has an effect of unopposed alpha vasoconstriction resulting from blockade of beta receptors. It also causes reduction in portal inflow as it lowers the cardiac output, heart rate and contractility. Hence it can be a better choice than propranolol.[9] In Pakistan hepatitis C related cirrhosis is notuncommon. The most frequent presentation of the patients is upper gastrointestinal bleeding. This bleeding is secondary to variceal bleeding and thrombocytopenia. Hence the purpose of this study is to observe the effect of carvedilol on low platelet count in patient's withportal hypertension& hepatitis C related cirrhosis. As it is obvious from the results of a study that carvedilol reduces the portal hypertension in a better way than other beta blockers[12] and so it is proposed that in turn it may be effective to correct thrombocytopenia. Therefore it is likely to decrease the morbidity and mortality related to upper gastrointestinal bleeding and the need for repeated hospitalizations as well as treatment cost will also be cut down.

METHODS

A descriptive study was done in the Department of Gastroenterology, Fatima Memorial Hospital, Lahore. In a period of six months from 17th October 2015 to 16th April 2016 a total of one hundred and fifty cases of Hepatitis C related cirrhosis associated splenomegaly and thrombocytopenia were included in the study through a convenient sampling. ELISA was used to diagnose all patients with hepatitis C. However cirrhosis & splenomegaly were diagnosed on ultrasound. Patients with platelet count of less than 100,00/ mm3 were included in the study. However, those with pregnancy, heart rate of less than 60/min were excluded from the study. An informed and signed consent was taken. After a detailed history, a complete physical examination was carried out with particular emphasis on the patient's blood pressure and resting heart rate. All patients were guided for hematological investigations. Blood samples were drawn at first presentation and anti-coagulated blood was used to determine baseline platelet count. Platelet count was checked using the Caulter counter. The patients were given carvedilol and its dose was adjusted so as to achieve a 25% reduction in baseline heart rate. Their blood pressure was again recorded after target heart rate achieved. After 2weeks of achieving the required heart rate, a platelet count was repeated. It was decided to continue carvedilol in all patients even after completion of the study because the drug has been known to improve portal hypertension. All the above information was collected on a proformas.

RESULTS

A total of 150 patients were included in the study. The mean age was 51.9 ± 8.88 years. Majority of the patients were 41 to 50 years of age. The males were 62% and females were 38%. Gradual increase in abdominal girth was seen in 49% patients and pedal edema was also seen in 49% patients. These two clinical features were the most common presenting complaints seen followed by pain epigastrium and vomiting which had 40% frequency. Fever and generalized abdominal pain was seen in 27% patients. However 14% patients presented with symptoms other than those mentioned in Table-I. The mean systolic blood pressure before and after treatment with carvedilol was135 (±11.5, $p<0.05$) and 117 (±10.6, $p<0.05$). 17 (± 6.6, $p<0.05$) was the mean difference in systolic blood pressure. As far as the mean diastolic blood pressure before and after treatment with carvedilol is concerned it was found to be 84 (± 7.2, $p<0.05$) and 75 (± 7.5, $p<0.05$) respectively. The mean difference was 8 (± 5.2, $p<0.05$) 101 ± 8.3and 90± 8.4 ($p<0.05$) was the mean arterial blood pressure before and after treatment with carvedilol was respectively. The mean difference was 11.5 (± 5, $p<0.05$). Similarly96 (± 9.3, $p<0.05$) and 76(± 7.6, $p<0.05$) respectively, was the mean pulse before and after treatment with carvedilol. (Table-II) The mean difference however was 20 (± 6.6$p< 0.05$).

Sixty six percent (66%) of patients responded to carvedilol therapy (Table-II). After treatment with carvedilol the mean platelet count before and after was 62 (±21, $p<0.05$) and 78(±25 $p<0.05$) respectively. Mean difference in was 16 (± 10.3 $p< 0.05$). (Table-V). A 12.5mg of carvedilol was requiredin 65 patients to achieve target heart rate.

Mean dose required was 19.37±5.76 (Table-III). Correlation coefficients as shown in Table-IV for change in platelet count with change in systolic blood pressure, pulse and dose required was significant ($p<0.05$) but those with diastolic blood pressure and mean arterial blood pressure was not ($p>0.05$)

Presenting complaints	Percentage
Increasing Abdominal Distension and Pedal edema	49
Pain epigastrium and vomiting	40
Generalized Abdominal pain and fever	27
Bleeding tendencies	18
Deepening of jaundice and drowsiness	16
Total	150

Table-I. Frequency of presenting complaints

Variable	Pre treatment	Post treatment	Signi-ficance
Systolic blood pressure	135±11.5	117±10.6	<0.05
Diastolic blood pressure	84±7.2	75±7.5	<0.05
Mean arterial blood pressure	101±8.3	90±8.4	<0.05
Pulse	96±9.3	76±7.6	<0.05
Platelet count	62±21	78±25	<0.05

Table-II. Comparison of means and two-tailed paired sample T-Test

Blood Pressure in mmHg; Pulse: in beats per min Platelets count: 1000/microlitre

Dose of Carvedilol (mg)	Frequency
3.125	14
6.25	45
12.5	65
25	19
50	7
Total	150

Table-III. Dose of Carvedilol

Mean dose 19.37±5.76

	Change in Platelet Count	
	Pearson Correlation	Significance
Change in systolic blood pressure	0.207	0.05
Change in diastolic blood pressure	0.087	0.414
Change in mean arterial blood pressure	0.149	0.158
Change in pulse	0.244	**0.02**
Dose of carvedilol	0.322	**0.002**

Table-IV. Correlations of Change in Platelet Count

Blood pressure in mmHg. Pulse, in beats per minute. Platelet count in 1000/microlitre

Changes in Platelet Count (>15% from baseline)	Frequency	Percentage
Increased	99	66%
No change	45	30%
Decreased	6	4%

Table-V. Frequency of Changes in the Platelet Counts

DISCUSSION

A total of one hundred and fifty patients were included in this study. They had liver cirrhosis due to Hepatitis C, leading to portal hypertension and splenomegaly. Such patients frequently present with upper gastrointestinal bleeding secondary to variceal bleeding and thrombocytopenia. The objective of this study is that carvedilol might improve the platelet counts in cirrhotic patients. The morbidity and mortality due to upper gastrointestinal bleeding is likely to get corrected if thrombocytopenia is treated. This will lead to cut down the need for repeated hospitalizations. The mean age of the patients was 51 ± 8.88 years however Sakai K et al[14] found the mean age of a total of 19 patients in their study to be 62 ± 3 years. A total of 62% patients were male and 38% were female in comparison to Sakai K et al[14] in which they had 57% male and 43% female patients. The difference in systolic blood pressure after treatment with carvedilol was 17.03±6.58 in comparison with the fall in diastolic blood pressure by 8.83±5.27. A sudden

fall in systolic blood pressure is due to the direct negative chronotropic effect of carvedilol on the beta-1 receptors in the heart. Similarly there was a significant reduction in heart rate after the administration of carvediloldue to the direct effect of this drug on the sinoatrial and atrioventricular nodes in the heart hence producing a negative chronotropic effect on the heart. The difference in mean arterial blood pressure; calculated by the formula 1/3 pulse pressure + diastolic blood pressure, remains significant $p<0.05$. In contrast, Sakai K et al[14] showed that there was a significant reduction ($p<0.05$) in heart rate with carvedilol and the mean arterial blood pressure. This difference might be due to the larger sample size in our study as compared to 19 patients studied by Sakai K et al.[14]

Beta-2 adrenoceptors are located in the splanchnic circulatory system. According to Sakai K et al[14] the changes in splenic circulation in the arteries with use of beta blockers were similar to the changes produced in the mesenteric arterial circulation. This was also shown by Iwao T et al.[15] The mechanism behind this might be unopposed α vasoconstriction resulting from the blockade of β-2 receptors. In this study, there was a significant increase in platelet count after administration of carvedilol. The change in platelet count is significantly correlated by the changes in intrasplenic and extrasplenic arterial pulsatility indices (Sakai K et al[14]) These findings suggest that the platelet count is in part, regulated by the splenic arterial hemodynamics. This idea is further supported by the finding that thrombocytopenia is ameliorated after transarterial splenic arterial embolization[16,17] which actually increases splenic arterial vascular resistance.

In this study, after carvedilol administration, the variation in response of platelet count can be explained by the individual variation in response of the splenic artery to carvedilol, which may be due to a difference in the number of β-2 receptors in the splenic artery. Portal hypertension causes congestive splenomegaly, which in turn causes the pooling of platelets. Thus reduction in the portal pressure induced by carvedilol may further decrease the platelet pool in the spleen.[13] Indeed, it has been shown that portal decompressive procedures such as surgical portosystemic shunts[18,19] and transjugular intrahepatic portosystemic shunts[20] ameliorate thrombocytopenia in patients with cirrhosis. It further needs to be assessed if there is any modification of the immunological factors such as PA-IgG and thrombopoeitin production by carvedilol administration. Thus future study is needed to test this point.

CONCLUSION

1) Carvedilol improves the thrombocytopenia in cirrhosis.
2) Rise in Platelet count is inversely proportional to the pulse.
3) Pulse can be used as an indirect measure of adequate beta blockade in the splanchnic circulation.

RECOMMENDATIONS

It is recommended that Further studies with longer duration of follow up must be carried out to watch for sustained response of carvedilol on thrombocytopenia and for incidence of first variceal bleed in patients on carvedilol.

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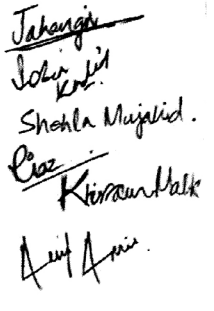
1	M. Jahangir Mujahid	Conception, Design & Acquisition of data.	
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