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ORIGINAL ARTICLE

Effect of Simvastatin on Hepatic Venous Portal Gradient for Maintenance of Lipid Profile of Liver Cirrhosis patients

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ABSTRACT

Background: Liver cirrhosis has an essential influence on the lipid profile. Statins have well-known beneficial cardiovascular effects reducing cardiovascular events and mortality.
Aim: To compare the change in hepatic venous portal gradient with or without simvastatin for maintenance of lipid profile of liver cirrhosis patients
Methods: This Randomized controlled trial was done at Department of Medicine, South medical ward, Mayo hospital, Lahore from October 2021 to March 2022.patients were randomly divided in two groups. In group A, patients were given simvastatin with standard treatment. In group B, patients were given standard treatment only. Before and after 1 month of treatment, lipid profile and HVPG level were assessed again. The change in HVPG and lipid profile was calculated. Data was entered and analyzed in SPSS version 25.
Results: The mean age of patients received simvastatin was 55.26 ± 13.24 years and mean age of patients in control was 53.74 ± 16.88 years. In simvastatin group, there were 82 (54.7%) males and 68(45.3%) females. In control group, there were 93 (62.0%) males and 57(38%) females. With simvastatin, the mean HVPG level was reduced from 20.11± 6.21mg/dl to 15.42±4.71 mg/dl after a month (mean change = 4.69 ± 1.50 mg/dl). While in control group, mean HVPG level was reduced from 19.28±7.61 mg/dl to 17.82± 6.52 mg/dl after a month (mean change = 1.46±1.09 mg/dl). The effect size was 23.3% with simvastatin while 7.6% without simvastatin for reduction of HVPG in cirrhotic patients. The difference was observed to be significant ($p<0.05$).
Conclusion: Thus, addition of simvastatin is effective in controlling lipid profile of patients with liver cirrhosis. It also has beneficial role in improving condition of liver cirrhosis patients.
Keywords: hepatic venous portal gradient, simvastatin, lipid profile, liver cirrhosis, LDL, HDL, total cholesterol, triglycerides

INTRODUCTION

A wide range of illnesses, including idiopathic, viral, hereditary, drug- and toxin-induced, autoimmune, and genetic disorders are all referred to as chronic liver disease [1]. Cirrhosis is a frequent result of ongoing liver injury. As a result of the build up of extracellular material, such as type I collagen activated by hepatic stellate cells and myofibroblasts, normal liver tissue is replaced by fibrotic tissue[2].

Worldwide, chronic liver disease causes over 2 million fatalities each year. Hepatocellular carcinoma and cirrhosis complications are the 11th and 16th most frequent causes of mortality, respectively, because they result in the majority of fatalities [3]. In the general population, dyslipidemia is prevalent and raises the risk of cardiovascular disease. Dyslipidemia can be treated, which reduces cardiovascular disease morbidity. Statins and other drugs for dyslipidemia target genes in the liver because it is the main generator of cholesterol and other lipids in the body. Additionally, the liver is involved in the metabolism of a variety of medications, including those used to treat dyslipidemia. Therefore, it is not unexpected that many medical professionals are reluctant to recommend medications to treat dyslipidemia in liver disease[4,5].

Statins, which are frequently used to decrease cholesterol, work by competitively inhibiting the enzyme 3-hydroxy-3-methylglutaryl coenzyme. It is being prevented from becoming mevalonic acid by a reductase. One of the cornerstones of both the primary and secondary prevention of atherosclerotic cardiovascular disease is statin therapy[6,7]. With more than 200 million users worldwide and 30 million users in the USA, they have well-known positive cardiovascular effects lowering cardiovascular events and mortality[8].

Rationale of this study is to compare the change in HVPG with or without simvastatin for maintenance of lipid profile of liver cirrhosis patients. Literature showed that addition of statins for maintenance of lipid profile in cirrhotic patients is safe and can help to reduce HVPG level in cirrhotic patients, thus can help to prevent esophageal varices and complication of cirrhosis and portal hypertension. But not much work has been done before in this regard. Also there is no study done in Pakistan before, in this regard which can help us to implement ore effective treatment regimens for cirrhotic patients. Therefore, we want to conduct this study to get reliable results, which can be implemented, in local setting and results can be implemented to apply more appropriate method for maintenance of lipid profile of cirrhotic patients to reduce the chances of portal hypertension and esophageal varices as well.

The objective of the study was to compare the change in hepatic venous portal gradient with or without simvastatin for maintenance of lipid profile of liver cirrhosis patients.

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MATERIALS AND METHODS

This randomized controlled trial was conducted in the Department of Medicine, South Medical ward, Mayo hospital, Lahore from 1st October 2021 to 31st March 2022 for 06 months. Sample size was 300 cases; 150 in each group were calculated with 5% significance level, 90% power of study and percentage reduction in HVPG i.e. 7.6% with statins and 1.5% without statins[9]. Consecutive (Nonprobability) Sampling technique was used. Patients of age ranged 20 to 70 years, both gender, diagnosed with liver cirrhosis, which was defined as coarse liver detected on ultrasound. Patients with total cholesterol level >150 mg/dl were included in the study. Patients already taking statins or having total cholesterol <100 mg/dl, taking steroids therapy within 3 months before enrolment, taking fabric acid agents, niacin, omega acid ethyl esters, thyroid hormones (on medical record) that could influence their lipid profile were excluded.

Data Collection Procedure: After approval of research project from the ethical board, 300 patients fulfilled the inclusion criteria were recruited form OPD of Department of Medicine, South Medical Ward, Mayo Hospital, Lahore. Informed written consent

was taken from each patient. Demographics was also taken on proforma. Blood sample was taken by using 3cc disposable syringe with the help of a staff nurse. All samples were sent to the laboratory of the hospital for assessment of lipid profile. Meanwhile, patient underwent minimally invasive fluoroscopy-guided procedure and HVPG level was recorded. Then patients were randomly divided in two groups by using random number table. In group A, patients were given simvastatin 20 mg/day for 1 month (increased to 40 mg/day at day 15) along with standard treatment of cirrhosis. In group B, patients were given standard treatment only. Then patients were followed-up in OPD for 1 month. After one month, blood sample was taken to assess the lipid profile and minimally invasive fluoroscopy-guided procedure to detect HVPG level after treatment. The change in HVPG and lipid profile were calculated. Effect was calculated in terms of percentage reduction in HVPG level after 1 month of treatment as compared to baseline by using following formula: Percentage decrease =HVPG (Baseline) – HVPG (1month) / HVPG (baseline).

Data Analysis: Data was analyzed using SPSS version 25.0. Mean and standard deviation were calculated for numeric variables. Frequency and percentage were calculated for categorical variables. Both groups were compared for mean change in lipid profile and HVPG by using independent samples t-test and chi-square test were applied to compare the effect in both groups. P-value ≤ 0.05 was considered as significant.

RESULTS

In this study, we included total 300 patients of liver cirrhosis and were randomized in two groups. The mean age of patients received simvastatin was 55.26±13.24 years and mean age of patients in control was 53.74±16.88 years. In simvastatin group, there were 82(54.7%) males and 68(45.3%) females. In control group, there were 93(62%) males and 57(38%) females. The mean BMI of patients received simvastatin was 23.68±10.28 kg/m^2 and mean BMI of patients in control was 22.52±8.69 kg/m^2. The mean duration of cirrhosis received simvastatin was 2.08±0.47 years and mean duration of cirrhosis in control was 2.59±1.18 years. In simvastatin group, 43(28.7%) were smokers and in control group, 57(38%) were smokers. In simvastatin group, 43(28.7%) were smokers and in control group, 57(38%) were smokers. In simvastatin group, 77(51.3%) were hypertensive and in control group, 49(32.7%) were hypertensive. In simvastatin group, 96(64%) were diabetic and in control group, 108(72%) were diabetic. Out of 150 cases of simvastatin group, 50(33.3%) had Child-Pugh class A, 79(52.7%) had Child-Pugh class B and 21(14%) had Child-Pugh class C. Out of 150 cases of control group, 44(29.3%) had Child-Pugh class A, 98(65.3%) had Child-Pugh class B and 8(5.3%) had Child-Pugh class C (Table 1).

At baseline, the mean cholesterol level was 298.56 ± 52.18 mg/dl in simvastatin group, which was reduced to 200.31±44.17 mg/dl after a month, showing a mean change of 98.25± 8.01 mg/dl. While in control group, mean cholesterol level was reduced from 306.17±42.58mg/dl to 258.31±32.16mg/dl after a month, showing a mean change of 47.86±10.42mg/dl. The difference in both groups as significant (p<0.05). At baseline, the mean triglyceride level was 198.52±32.28 mg/dl in simvastatin group, which was reduced to 134.89 ± 22.17 mg/dl after a month, showing a mean change of 63.63±10.11 mg/dl. While in control group, mean triglycerides level was reduced from 187.55±36.57mg/dl to 156.99 ± 32.29 mg/dl after a month, showing a mean change of 30.56±4.28 mg/dl. The difference in both groups is significant (p<0.05). At baseline, the mean LDL level was 219.76±56.57mg/dl in simvastatin group, which was reduced to 147.28±34.59 mg/dl after a month, showing a mean change of 72.48±21.98 mg/dl. While in control group, mean LDL level was reduced from 229.91±58.54 mg/dl to 189.45±42.31mg/dl after a month, showing a mean change of 40.46±16.23 mg/dl. The difference in both groups as significant (p<0.05). At baseline, the mean HDL level was 25.63 ± 9.85 mg/dl in simvastatin group, which was increased to 46.96 ± 7.85 mg/dl after a month, showing a mean change of 21.33±2.00 mg/dl. While in control group, mean HDL level was improved from 26.32 ± 9.94mg/dl to 34.12 ± 7.21 mg/dl after a month, showing a mean change of 7.80±2.73 mg/dl. The difference in both groups as significant (p<0.05). At baseline, the mean HVPG level was 20.11±6.21 mg/dl in simvastatin group, which was reduced to 15.42 ± 4.71 mg/dl after a month, showing a mean change of 4.69±1.50 mg/dl. While in control group, mean HVPG level was reduced from 19.28 ± 7.61 mg/dl to 17.82 ± 6.52 mg/dl after a month, showing a mean change of 1.46 ± 1.09 mg/dl. The difference in both groups as significant (p<0.05). The effect size was 23.3% with simvastatin while 7.6% without simvastatin for reduction of HVPG in cirrhotic patients (Table 2).

Table 1: Baseline characteristics of patients

	Simvastatin Group	**Control Group**
n	150	150
Age (years)	55.26 ± 13.24	53.74 ± 16.88
Gender		
Male	82 (54.7%)	93 (62.0%)
Female	68 (45.3%)	57 (38.0%)
BMI	23.68 ± 10.28	22.52 ± 8.69
Duration of cirrhosis	2.08 ± 0.47	2.59 ± 1.18
History of:		
Smoking	43 (28.7%)	57 (38.0%)
Hypertension	77 (51.3%)	49 (32.7%)
Diabetes	96 (64.0%)	108 (72.0%)
Child-Pugh class		
A	50 (33.3%)	44 (29.3%)
B	79 (52.7%)	98 (65.3%)
C	21 (14.0%)	8 (5.3%)

Table 2: Comparison of lipid profile in patients who were given simvastatin versus control

	Group		**p-value**
	Simvastatin	**Control**	
Baseline	298.56 ± 52.18	306.17 ± 42.58	0.1675
1 month	200.31 ± 44.17	258.31 ± 32.16	<0.0001
Change	98.25 ± 8.01	47.86 ± 10.42	<0.0001
Triglycerides			
Baseline	198.52 ± 32.28	187.55 ± 36.57	0.0062
1 month	134.89 ± 22.17	156.99 ± 32.29	<0.0001
Change	63.63 ± 10.11	30.56 ± 4.28	<0.0001
LDL			
Baseline	219.76 ± 56.57	229.91 ± 58.54	0.1278
1 month	147.28 ± 34.59	189.45 ± 42.31	<0.0001
Change	72.48 ± 21.98	40.46 ± 16.23	<0.0001
HDL			
Baseline	25.63 ± 9.85	26.32 ± 9.94	0.5393
1 month	46.96 ± 7.85	34.12 ± 7.21	<0.0001
Change	21.33 ± 2.00	7.80 ± 2.73	<0.0001
HVPG			
Baseline	20.11 ± 6.21	19.28 ± 7.61	0.3016
1 month	15.42 ± 4.71	17.82 ± 6.52	0.0003
Change	4.69 ± 1.50	1.46 ± 1.09	<0.0001
Effect	23.3%	7.6%	

DISCUSSION

Cirrhosis of the liver is a fatal disorder. It stores and metabolizes the lipid. Cirrhosis of the liver significantly affects the lipid profile[10]. Though cirrhosis was once believed to prevent atherosclerotic disease, research in recent years has shown that people with cirrhosis may have a higher prevalence of coronary artery disease than the general population[11].

Statins may be helpful in treating various chronic inflammatory disorders due to their pleiotropic effects, which include reducing cholesterol levels as well as having anti-inflammatory, antiangiogenic, and anti-fibrotic properties. Because of worries about their safety in patients with reduced liver function, statins have only lately been looked into as a viable therapy option for chronic liver illnesses. Numerous research projects using

animal models of liver illnesses have demonstrated that statins reduce hepatic fibrogenesis, inflammation, and portal pressure[12].

Patients with Child-Pugh class A cirrhosis can safely utilise statins. The safety and hazards of statin use in patients with decompensated cirrhosis are poorly or completely unknown. The Liver Expert Panel's updated 2014 recommendations, which were created to address the safety of statins in liver disease, offer some guidance and discourage the use of statins among people who have Child-Pugh class B or C cirrhosis[13].

Muscle damage is the most frequent side effect of statins, which are among the safest drugs for lowering cholesterol. Hepatotoxicity and newly developed diabetes mellitus are further negative consequences[14,15]. In our study, we observed that at baseline, the mean HVPG level was 20.11 ± 6.21 mg/dl in simvastatin group, which was reduced to 15.42 ± 4.71 mg/dl after a month, showing a mean change of 4.69 ± 1.50 mg/dl. While in control group, mean HVPG level was reduced from 19.28 ± 7.61 mg/dl to 17.82 ± 6.52 mg/dl after a month, showing a mean change of 1.46 ± 1.09 mg/dl. The difference in both groups as significant ($p<0.05$). The effect size was 23.3% with simvastatin while 7.6% without simvastatin for reduction of HVPG in cirrhotic patients.

Short-term statin therapy affected hepatic portal channel pressure metrics. Treatment with statins improved the prognosis of liver cirrhosis during long-term monitoring. It is confirmed that statins are safe and effective for treating liver cirrhosis[16]. According to a study, using statins caused a percentage decrease in HVPG of -8.3%, whereas not taking them caused a change of 0%[17]. In a different trial, mean HVPG was found to have decreased from 18.5 mmHg to 17.1mmHg (a 7.6% change), while with placebo, it increased from 19.8mmHg to 19.5mmHg (a 1.5% change)[9]. The results of one more experiment revealed that the mean HVPG had decreased from 16.752.12mmHg to 13.0291.56mmHg (a reduction of 22.2%)[18].

CONCLUSION

Thus, addition of simvastatin is effective in controlling lipid profile of patients with liver cirrhosis. It also has beneficial role in improving condition of liver cirrhosis patients. In future, we can now be able to recommend the addition of simvastatin to maintain the lipid profile of cirrhotic patients.

Conflict of interest: Nothing to declare

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