Original Article

Comparing the Effects of Rosuvastatin and Silymarin on Lipid Levels as Monotherapy or Combination Therapy for the Treatment of Hyperlipidemia

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ABSTRACT

Objective: To evaluate the effects of silymarin alone or in combination with rosuvastatin on elevated total cholesterol, Triglycerides, high levels of Low Density lipoproteins and low levels of High Density Lipoproteins.
Study Design: Randomized open clinical trial study
Place and Duration of Study: This study was conducted at the National Medical Center, Karachi from October 2020 to March 2021 for a period of six months.
Materials and Methods: 90 Hyperlipidemic males and females age group 40≥ and ≤75 years were allocated into three groups of 30 subjects each by computer allocated balloting randomization. The Group A subjects were given Tablet Rosuvastatin 10mg OD alone. The Group B subjects were given Tablet Rosuvastatin 10mg OD and Tablet Silymarin 200mg 1× BD. The Group C subjects were advised Tablet Silymarin 200mg 1×BD alone for the period of 3 months. Baseline investigations FLP, LFTS and CPK were done at week 0 and at week 12. There were total three visits of patients, at week 0, at week 6 and at the end of week 12.
Results: Rosuvastatin and Silymarin are consistent in decreasing the lipid levels at week 12 when compared with the baseline. Silymarin also shows good result in decreasing liver enzymes and CPK levels significantly.
Conclusion: Silymarin shows great potential in decreasing lipid levels of the blood when used alone and in combination with rosuvastatin. It has also shown great results in decreasing liver enzymes when used alone or in combination with rosuvastatin. The results of this study can further be evaluated with bigger sample size.
Key Words: Hyperlipidemia, Triglycerides, Low Density Lipoproteins, High Density Lipoproteins, Rosuvastatin, Silymarin

Citation of article: Zubair MZ, Mansoor M, Hoor T, Amjad H, Jaffri MSA, Tahir MA. Comparing the Effects of Rosuvastatin and Silymarin on Lipid Levels as Monotherapy or Combination Therapy for the Treatment of Hyperlipidemia. Med Forum 2021;32(12):43-47.

INTRODUCTION

Hyperlipidemia is an umbrella term that deals with various genetic or acquired disorders characterized by elevated serum levels of lipoproteins mainly very low-density lipoprotein, low density lipoprotein and Low levels of high-density lipoprotein[1]. It is also associated with elevated levels of triglycerides, cholesterol and cholesterol esters.

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Received: August, 2021
Accepted: October, 2021
Printed: December, 2021

Increase in cholesterol levels and triglyceride level leads to atherosclerosis which is intimal thickening, lipid accumulation and calcification in the arteries causing endothelial dysfunction and can result in cardiovascular diseases[2]. Rosuvastatin, a HMG CoA reductase inhibitors have been approved as a first line Drug for Hyperlipidemia and significantly decrease high levels of cholesterol, TG and LDL[3]. Statins are usually well tolerated but it has certain adverse effects including gastrointestinal tract disorders, musculoskeletal pain, infections related to respiratory tract, headaches and lack of adherence give rise to depleted outcomes which causes shift towards the alternative therapies[4,5].

Silymarin, a traditional herbal remedy obtained from the seed of silybum marianum also known as milk thistle plant. It belongs to the largest family of kingdom plant Asteraceae and is epidemic in the Mediterranean and North African regions but can be also be found in North West areas of Pakistan[6] and all the temperate areas around the globe. It is a complex mixture having an empirical formula $C_{25}H_{22}O_{10}$[7] and is composed of ample flavonolignans, out of them silibinin is the most

essential component and composed of two diastereomers silibinin A and silibinin B thought to be responsible for the biological activity of silymarin[8]. Other flavonoligams includes silibinin, isosilibinin, silydianin, silychristin, isosilychristin, silimonin[9]. Besides Flavonolignans it also contains several flavonoids which includes taxifolin, quercetin, dihydrokaempferol, kaempferol, apigenin, naringin, eriodyctiol, and chrysoeriol. Silymarin has been used as a remedy since ancient times. For about 2000 years, its been used as an herbal medicine for many types of hepatic and gallbladder disorders of acute and chronic nature[10]. Silymarin can have a major role in decreasing lipid profile in patients of hyperlipidemia[11] as it is affiliated with alteration of membrane lipid by interfering with the secretion and uptake of lipoproteins Various studies show beneficial effects on LDL cholesterol. It is said that that it can be used alone or in combination with other anti-hyperlipidemic drugs to reduce the levels of TC, TG, LDL and increases the levels of HDL cholesterol in the blood[12].

MATERIALS AND METHODS

It is a randomized open clinical trial that was conducted in 130 males and females ≥ 40 and ≤75 years of age diagnosed with hyperlipidemia with fasting lipid profile TC ≥ 200, LDL ≥ 100 mg/dl, Triglycerides ≥ 150 and BMI ≥28 associated with either Diabetes, Hypertension, Hypothyroidism or Ischemic heart disease were inducted in the study after a written informed consent. Patients with age < 40 and >75 years, having myopathies, having raised CPK levels, BMI < 28, pregnant woman and lactating mothers were excluded from the study. Recruitment of patient was done from OPD of National Medical Center. Out of these 130 patients only 90 patients completed the study which were allocated into three groups of 30 patients each by a computer allocated balloting randomization. The Group A subjects were given Tablet rosuvastatin 10mg OD alone. The Group B subjects were given Tablet Rosuvastatin 10mg OD and Tablet Silymarin 200mg 1× BD. The Group C subjects were advised Tablet Silymarin 200mg 1×BD alone for the period of 3 months. Baseline investigations FLP, LFTS and CPK were done at week 0 and at week 12. There were total three visits of patients, at week 0, at week 6 and at the end of week 12. At week 0 patients were asked to read consent form and sign it, they were assessed for anthropometric measurements, evaluation form was filled with personal and laboratory data and were advised to take low carbohydrate and low fat diet. At week 6 the patients were called to check for any adverse symptoms and check their compliance and after 12 weeks patients were called along with the laboratory investigation reports. At this time their anthropometric measurements were also checked and documented.

RESULTS

90 patients of Hyperlipidemia completed the study and divided equally into three groups Group A, Group B and Group C. The mean age of the patients included in the study was 50.61±8.150. The population of female was more as compared to males and majority of them were married.

Anthropometric measurements: Weight, height, waist and hip circumference were noted at 0 week and at 12th week. BMI and Waist Hip ratio was calculated. The mean BMI of the patients was found to be 34.1±7.71 and mean waist ratio was found to be 0.93 for all 90 patients.

Laboratory Findings

Lipid profile: The paired analysis between day 0 and day 90 of all 3 groups for the lipid profile parameters was done which includes total cholesterol, triglycerides, high density lipoprotein cholesterol and low-density lipoprotein cholesterol was performed by Paired Students t test.

Total cholesterol: The levels of total cholesterol were recorded at week 0 and at week 12. The results for Group A, B and C is significant having p value less than 0.001.

Triglycerides: The levels of triglycerides were recorded at week 0 and at week 12. The results for Group B and C is significant having p value less than 0.001 while p value for group C is 0.038 which is non-significant.

Low density lipoprotein cholesterol: The comparison between day 0 and day 90 of LDL levels between 3 groups and the results were significant for all three groups having p value less than 0.001.

High density lipoprotein cholesterol: HDL levels were marked at day 0 and at day 90 of the study. The results for group A and B were non-significant having p values 0.857 and 0.684 respectively. Group C showed highly significant results having p value less than 0.001.

Liver function tests: The comparison between day 0 and day 90 of the treatment group for liver function tests which include SGPT and SGOT was done by paired student T test.

Serum Glutamic Pyruvic Transaminase: SGPT was done to assess the liver function and also to see the effects of drugs. All three groups showed significant result having p value 0.025, 0.005 and < 0.001 for group A, B and C respectively.

Serum Glutamic-Oxaloacetic Transaminase: SGOT levels were marked at day 0 and at day 90 of the study All three groups showed significant results having p values < 0.001, 0.026 and < 0.001 for group A, B and C respectively.

Creatine Phosphokinase: CPK levels were marked at day 0 and at day 90 of the study. The results for group A was 0.054 which is non-significant and got significant results for group B and C having p values 0.012 and <.001 respectively. (Table 1 to 3 & Figure 1).

Table No.1: Association of Clinical variables at the time of admission among different groups

Variables		Group		
		Group A (Rosuvastatin	Group B (Rosuvastatin+Silymarin)	Group C (Silymarin)
Age(years)	40-51	14(46.7%)	17(56.7%)	23(76.7%)
	52-63	10(33.3%)	10(33.3%)	7(23.7%)
	64-75	6(20%)	3(10%)	0(%)
Gender	Female	18(60%)	19(63.3%)	19(63.3%)
	Male	12(40%)	11(36.7%)	11(36.7%)
BMI	Baseline	35.647±12.28	33.704±4.88	32.943±1.82
	3 Months	33.297±3.65	33.237±4.82	32.407±1.77
Waist Hip Ratio	Baseline	0.9330± 0.038	0.9347±0.046	0.9393±0.016
	3 Months	0.9343±0.030	0.9410±0.028	0.9433±0.016
Marital Status	Married	29(96.7%)	28(93.3%)	30(100%)
	Unmarried	1(3.3%)	2(6.7%)	0(%)
Diabetes	Yes	23(76.7%)	23(76.7%)	29(96.7%)
	No	7(23.3%)	7(23.3%)	1(3.3%)
Hypertension	Yes	15(50%)	15(50%)	14(46.7%)
	No	15(50%)	15(50%)	16(53.3%)
Hypothyroidism	Yes	3(10%)	2(6.7%)	0(%()
	No	27(90%)	28(93.3%)	30(100%)
IHD	Yes	2(6.7%)	2(6.7%)	3(10%)
	No	28(93.3%)	28(93.3%)	27(90%)

Table No.2: Group variables

	Group	Variables	Mean±STD	P-value
Group A (n=30)	Baseline	Pre TC mg/dl	220.17±37.929	
	3 months	Post TCmg/dl	180.23±27.656	<.001*
	Baseline	Pre TG mg/dl	194.47±63.35	
	3 months	Post TG mg/dl	163.17±56.37	0.038*
	Baseline	Pre LDL mg/dl	120.83±35.276	
	3months	Post LDL mg/dl	98.40±16.188	<.001*
	Baseline	Pre HDL mg/dl	37.80±8.536	
	3 months	Post HDL mg/dl	37.90±7.915	0.857
Group B(n=30)	Baseline	Pre TC mg/dl	215.33±50.174	
	3 months	Post TCmg/dl	181.07±40.299	<.001*
	Baseline	Pre TG mg/dl	191.87±73.629	
	3 months	Post TG mg/dl	154.83±60.428	<.001*
	Baseline	Pre LDL mg/dl	122.03±27.456	
	3 months	Post LDL mg/dl	101.17±21.651	<.001*
	Baseline	Pre HDL mg/dl	39.03±20.280	
	3 months	Post HDL mg/dl	37.67±6.440	0.684
Group C(n=30)	Baseline	Pre TC mg/dl	243.97±33.970	
	3 months	Post TC mg/dl	212.63±28.847	<.001*
	Baseline	Pre TG mg/dl	170.07±12.682	
	3 months	Post TG mg/dl	155.73±11.246	<.001*
	Baseline	Pre LDL mg/dl	112.03±13.142	
	3 months	Post LDL mg/dl	100.90±11.093	<.001*
	Baseline	Pre HDL mg/dl	35.03±4.375	
	3 months	Post HDL mg/dl	37.03±4.473	<.001*

Table No.3: Effect on Liver Function Test and CPK

Group	Variables	Mean±STD	P-value
Group A (n=30)			
Baseline	Pre SGPT mg/dl	26.30±14.898	
3 months	Post SGPTmg/dl	22.27±7.051	0.025

Baseline	Pre SGOT mg/dl	27.37±7.083	
3 months	Post SGOT mg/dl	25.53±6.415	<.001*
Baseline	Pre CPK units/L	51.57±24.54	0.054
3 months	Post CPK units/L	46.67±16.01	
GroupB(n=30)			
Baseline	Pre SGPT mg/dl	32.67±15.979	
3 months	Post SGPTmg/dl	27.63±12.0	0.005
Baseline	Pre SGOT mg/dl	31.30±12.669	
3 months	Post SGOTmg/dl	28.57±12.065	0.026
Baseline	Pre CPK units/L	53.77±29.84	
3 months	Post CPK units/L	50.10±27.93	0.012*
Group C(n=30)			
Baseline	Pre SGPT mg/dl	46.10±21.07	
3 months	Post SGPTmg/dl	38.20±13.535	<.001*
Baseline	Pre SGOT mg/dl	34.50±6.458	
3 months	Post SGOTmg/dl	32.07±5.919	<.001*
Baseline	Pre CPK units/L	36.40±14.03	
3 months	Post CPK units/L	34.90±13.51	<.001*

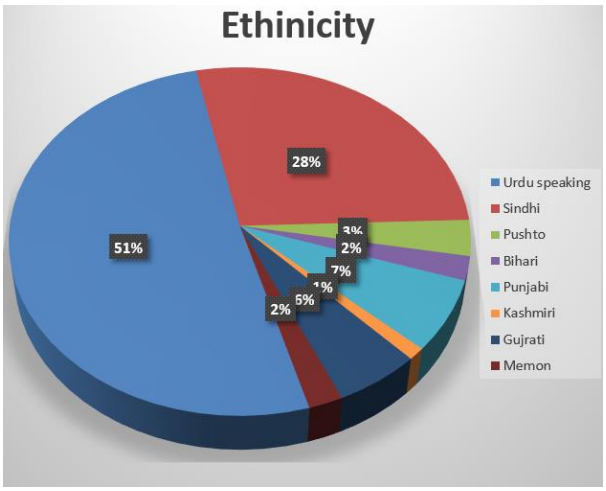

Figure No.1: Ethnicity of study population

DISCUSSION

This study was conducted to evaluate the effects of Rosuvastatin and Silymarin on blood levels of total Cholesterol, Triglycerides, LDL and HDL in hyperlipidemic patients and also focuses on the effect of these drugs on liver enzymes and CPK levels. As Rosuvastatin has established role in decreasing lipid levels but in this trial Silymarin has proved itself in decreasing lipid levels comparative to Rosuvastatin.

Decrease in Levels of Lipid profile in Rosuvastatin group is consistent with Liu which states decrease in levels of total cholesterol by 26% with the use of Rosuvastatin 10mg for 4 weeks and 31% reduction when given for 8 weeks with the sample size of 64 patients[13] and also Bostan which states the reduction in the levels of total cholesterol along with the reduction in levels of LDL, Apo E protein and Homocysteine. It has a sample size of 100 patients and they were given Tablet Rosuvastatin 20 mg for 6 months[14].

Decrease in Levels of Lipid profile in Rosuvastatin and Silymarin group is consistent with Abdul conducted the study on Silymarin and lovastatin with 45 patients altogether which was done to evaluate the effects of Silymarin on hyperlipidemia with different etiologies and gives significant result which shows the synergistic effect of Silymarin with statins in lowering down cholesterol levels[12].

Decrease in Levels of Lipid profile in Silymarin group is consistent with Hayder who conducted the study with 20 patients divided into 2 groups giving 600mg sugar as placebo and 600mg Silymarin for the period of 2 weeks[15] and also with Nauman who conducted a study to evaluate the effect of Silymarin 200mg BD on Type 1 diabetic patients who have poor control over insulin. This study along with other benefits also gives significant results in lowering TC levels compared with control group after 60 days. These results are consistent with the results of this study[16].

SGPT and SGOT were done to assess the liver function and also to see the effects of drugs. Rosuvastatin significantly decreases SGPT and SGOT levels which was significant with Nakahara[17]. Combination of Rosuvastatin and Silymarin also significantly decreases the liver enzymes which was consistent with Abdul[12]. Silymarin Group showed significant result in decreasing liver enzymes which was consistent with studies conducted by Hussein[18], Wah Kheong[19] and Ghalandari[20].

CONCLUSION

Natural products such as Silymarin when given in a dose of 200 mg BD for the period of 3 months can be a good alternative to high dose statins in order to

decrease lipid profile as a monotherapy along with decreasing SGPT and SGOT levels and also as combination therapy to avoid high doses of statins and provide good control on increased lipid levels specially in patients associated with co morbidities like Diabetes, Hypertension, Hypothyroidism and Ischemic heart disease. It is considered as a safe drug as there was no adverse effect associated with its use in our study.

Recommendations: Silymarin has vast range of therapeutic uses. Many trials can be done with a bigger sample size to evaluate its effect on lipids with different statins and other lipid lowering drugs, its role in glycemic control, hepatic protection, different liver diseases, in different poisoning cases, as a chemotherapeutic agent and also as anti-neurodegenerative agent.

Author's Contribution:

Concept & Design of Study:	Muhammad Ali Zubair
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Final Approval of version:	Muhammad Ali Zubair

Conflict of Interest: The study has no conflict of interest to declare by any author.

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