Original Article

Comparison Between Atorvastatin and Rosuvastatin on Anti-Thrombogenic Effect in Patients with Hyperlipidemia

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Abstract

***Background**: Atorvastatin and rosuvastatin are two widely used HMG-CoA reductase inhibitors (statins). These are used as lipid-lowering drugs to reduce atherosclerosis-induced cardiovascular events. The beneficial effects of statins also involve some lipid-independent mechanisms which include modification of thrombus formation and degradation, alteration in inflammatory response, plaque stabilization and improvement of endothelial function. **Objective**: To compare anti-thrombogenic effect of atorvastatin and rosuvastatin in patients with hyperlipidemia. **Materials and Methods**: A prospective, open-labeled, interventional, randomized and single-center study was carried out in Bangabandhu Sheikh Mujib Medical University (BSMMU), Dhaka from March, 2016 to August, 2017 on 52 hyperlipidemic patients. After randomization patients were assigned to atorvastatin 10 mg or rosuvastatin 5 mg daily for 8 weeks. Blood was collected at baseline and after intervention to measure platelet count, prothrombin time (PT) and serum lipid profile. **Results**: The baseline characteristics of patients treated with atorvastatin and rosuvastatin were almost identical. The platelet count in atorvastatin group was reduced after intervention (2.30%, p=0.463) which was not significant but in rosuvastatin group platelet count reduced significantly (12.33%, p=0.021) after intervention. There was no statistically significant difference (p=0.187) between the two statin treated groups. PT was increased significantly after intervention in both atorvastatin group (31.44%, p<0.001) and in rosuvastatin group (31.93%, p=0.003), which was statistically significant. No significant difference was observed between the two groups (p=0.573). Both atorvastatin and rosuvastatin significantly improved serum lipid profile. **Conclusion**: The present study reveals that rosuvastatin reduced thrombogenesis more effectively than atorvastatin in hyperlipidemic patients.*

***Key words**: Atorvastatin; Rosuvastatin; Thrombogenesis; Atherosclerosis*

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Introduction

Hyperlipidemia is an abnormal elevation of blood lipid concentration which contributes to the pathophysiology of atherogenesis and its grievous consequences like myocardial infarction (MI), ischemic stroke and peripheral vascular diseases (PVD).[1,2] Platelet activity has been enhanced in the presence of high LDL-cholesterol levels, leading to aggregation of platelet, thrombus formation and vascular occlusion.[3,4] There is increased activation of platelet in hyperlipidemic patients due to increased formation of thromboxane A_2 (TxA_2), a potent platelet aggregation activator.[5]

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ADP and ATP released from activated platelets cause further platelet aggregation and are recognized as major factors in the development of thrombosis.[6] Studies have suggested that along with lipid lowering effect HMG-CoA reductase inhibitor (statin) reduces cardiovascular complications by reducing thrombogenesis, oxidative stress, inflammation and improved endothelial function known as a 'pleiotropic effects' of statin.[7,8] Antithrombotic property is a vascular protective effect of statins, not related to changes in lipid profile. Studies have also shown that statins reduce platelet TxA_2 via down-regulation of phospholipase A_2 and inhibit platelet aggregation and that lead to anti-platelet aggregation effect.[9] However, it is still not clear whether all statins available share similar mechanisms of anticoagulant properties.[10]

Several drugs are included within the statin group, among them atorvastatin and now-a-days rosuvastatin are widely used. As there is no comparative study regarding anti-thrombotic effect of atorvastatin and rosuvastatin, the present study was planned to compare the anti-thrombogenic effects of newer emerging and promising rosuvastatin with existing commonly used atorvastatin in patients with hyperlipidemia and there by to guide the present treatment strategies.

Materials and Methods

This study was an 8-week randomized interventional open-labeled trial. This trial was approved by the Institutional Review Board (IRB) of Bangabandhu Sheikh Mujib Medical University (BSMMU) on 13th August, 2016. An approval number was collected (No. BSMMU/2016/8307). This study was also registered in ClinicalTrial.gov and study ID number was NCT02979704. Informed written consent was obtained from all participants. Patients were recruited from the outpatient department (OPD) of Cardiology, BSMMU. Eligible patients were randomized (by Online Random Number Generator & Checker) to receive once daily dose of 10 mg atorvastatin or 5 mg rosuvastatin for 8 weeks.[11]

The study population comprised 52 hyperlipidemic patients, both male and female[12], aged 20–75 years[13-15]. Eligibility criteria for randomized treatment included fasting LDL-C level >160 mg/dL and fasting triglyceride level <400 mg/dL.[16] Patients treated by other lipid lowering drugs[17], with history of smoking, alcohol intake[18] and hypersensitivity on any member of the statin group of drugs[17], taking anti-inflammatory medications[18], antioxidant vitamins (vitamins A, C, E)[19], anticoagulant or antiplatelet drugs[20], having impaired liver and/or renal functions[17,21], serious infections or terminal illness[22], pregnant women and nursing mothers[21] were not enrolled. Baseline measurements included levels of platelet count, prothrombin time (PT) and serum lipid profile with follow-up measurements after 8 weeks. With all aseptic precautions 5 mL blood was collected by venipuncture from the antecubital vein and kept it in 1 × 5 mL K_3EDTA (anticoagulant) containing test tube. Plasma was separated by centrifugation (3,500 rpm for 10 minutes) and stored at labeled microcentrifuge tube by micropipette, then stored at −20^{O}C in refrigerator (laboratory of Pharmacology Department, BSMMU) for measurement of PT and lipid profile until analysis. Platelet count was done by autoanalyzer and then rechecked manually in Department of Clinical Pathology, BSMMU. Patients were advised to take drugs at night before meals. Regularity of drug intake was ensured over telephone and from the patient's compliance sheet. Patients were asked to report any adverse effects of the medication given during the period of study. Patients were strictly advised to take fat-restricted diet.

Statistical analysis

Data were processed and recorded in Microsoft excel worksheet. Quantitative variables were expressed as mean ± SD. Differences in mean values between groups were assessed by using the two-tailed paired and unpaired Student's t-test. Data were analyzed with the help of Statistical Package for the Social Science (SPSS 16.0). The level of significance was set at p value less than 0.05.

Results

Table I shows the baseline demographic characteristics of all hyperlipidemic patients. There were total 21 males and 31 females. In atorvastatin group the age (mean ± SD) was 46.07 ± 10.47 years and in rosuvastatin group the age (mean ± SD) was 44.12 ± 8.34 years. Considering demographic characteristics, there was no significant difference at baseline between atorvastatin and rosuvastatin treated groups.

Table I: Demographic characteristics of subjects of both groups before intervention

Characteristics	Atorvastatin Group (n=27)	Rosuvastatin Group (n=25)	p values
Age (years)	46.07 ± 10.47	44.12 ± 8.34	0.740*
Sex			
Male	6 (22.22%)	15 (60%)	
Female	21 (77.78%)	10 (40%)	0.005ϕ
Body weight (kg)	69.74 ± 9.51	66.84 ±8.67	1.150*
Blood pressure:			
Systolic (mm Hg)	131.78 ± 16.38	135.20 ± 20.84	0.512*
Diastolic (mm Hg)	81.48 ± 9.88	85.80 ± 11.69	0.156*
Hypertension	13 (48.15%)	18 (72%)	0.080ϕ
Diabetes mellitus	2 (7.41%)	2 (8%)	0.936ϕ

n=number of patients in each group, values are expressed as mean ± SD, figures in the parentheses indicate corresponding %, ϕ Chi-squared test ($\chi 2$ was done to analyze the data),* data were analyzed by using unpaired t-test.

Before administration of drug, platelet count (mean ± SD) in atorvastatin group was 326.30 ± 62.61 × 10^9/L. After 8 weeks of treatment with atorvastatin the platelet count (mean ± SD) was decreased to 318.78 ± 74.94 × 10^9/L (Table II), which was not significant (p=0.463). On the other hand, baseline platelet count (mean ± SD) in rosuvastatin group was 328.80 ± 76.01 ×10^9/L and after intervention with rosuvastatin the platelet count (mean ± SD) was decreased to 288.24 ± 89.63 ×10^9/L (Table II), which was significant (p=0.021). No statistically significant difference was found in between two groups (p=0.187, Table II) after intervention. The mean decrease in platelet count in the atorvastatin treated group was 2.30% and in rosuvastatin treated group was 12.33% (Table II).

At baseline PT (mean ± SD) in atorvastatin and rosuvastatin groups were 11.07 ± 3.11 sec and 11.40 ± 3.38 sec. After 8 weeks of drug administration the PT was increased to 14.55 ± 2.63 sec in atorvastatin group and 15.04 ± 3.49 sec in rosuvastatin group (Table II). This change was statistically significant (p<0.001 and p=0.003 for atorvastatin and rosuvastatin group respectively, Table II). Again no statistical significant difference was found after intervention in between the statin treated groups (p=0.573, Table II) after intervention. The mean increase in PT in the atorvastatin treated group was 31.44% and in rosuvastatin treated group was 31.93% (Table II).

Table II: Thrombogenic biomarkers at baseline and after intervention

Variables	Atorvastatin Group (n=27)				Rosuvastatin Group (n=25)				p value*	p value**
	Before	After	p value#	% change	Before	After	p value#	% change		
Platelet count (× 10^9/L)	326.30 ± 62.61	318.78 ± 74.94	0.463	2.30↓	328.80 ± 76.01	288.24 ± 89.63	0.021	12.33↓	0.897	0.187
PT (Sec)	11.07 ± 3.11	14.55 ± 2.63	<0.001	31.44↑	11.40 ± 3.38	15.04 ± 3.49	0.003	31.93↑	0.718	0.573

n = number of patients in each group; values are expressed as mean ± standard deviation (SD), before = at baseline, after = after intervention, PT = prothrombin time, # = p in each group as compared to baseline (paired t-test), *= p of inter-group comparison at baseline (unpaired t-test), ** = p of inter-group comparison after intervention (unpaired t-test)

The level of serum total cholesterol (TC) was significantly reduced after intervention both in atorvastatin group (from 257.51 ± 21.82 mg/dL to 161.60 ± 39.59 mg/dL, 37.24%, p<0.001, Table III) and in rosuvastatin group (from 262.50 ± 38.72 mg/dL to 154.55 ± 35.47 mg/dL, 41.12%, p<0.001, Table III); but no statistically significant difference (p=0.503, Table III) was observed between the two statin-treated groups after intervention. Serum triglyceride (TG) level was reduced from 199.71 ± 80.65 mg/dL to 165.61 ± 75.47 mg/dL (17.07%, p=0.046, Table III) in atorvastatin group and from 198.89 ± 56.03 mg/dL to 145.59 ± 64.97 mg/dL (26.80%, p<0.001, Table III) in rosuvastatin group and these were statistically significant. No significant difference was observed between the two groups (p=0.312, Table III). The serum LDL-C level was reduced significantly from 178.16 ± 20.01 mg/dL to 89.11 ± 35.10 mg/dL, (49.98%, p<0.001) and from 181.57 ± 32.10 mg/dL to 85.91 ± 35.45 mg/dL, (52.68%, p<0.001) (Table III) in atorvastatin and rosuvastatin treated groups respectively. Again no statistically significant difference (p=0.749, Table III) was observed between the two groups after intervention. Both atorvastatin and rosuvastatin reduced serum HDL-C level (from 39.40 ± 9.56 mg/dL to 39.37 ± 11.51 mg/dL (0.08%, p=0.990) in atorvastatin group and from 41.14 ± 7.81 mg/dL to 40.41 ± 9.11 mg/dL (1.77%, p=0.696) in rosuvastatin group, Table III); but this reduction was not statistically significant. Inter-group difference was not significant (p=0.721, Table III).

Both atorvastatin and rosuvastatin were well-tolerated by patients of the present study. Two patients in atorvastatin group complained of abdominal discomfort and headache and one patient in rosuvastatin group complained of constipation. No serious adverse effects that needed dose adjustment or withdrawal of drug were seen in any subject.

Table III: Effect of atorvastatin and rosuvastatin on serum lipid profile

Variables	Atorvastatin Group (n=27)				Rosuvastatin Group (n=25)				p value*	p value**
	Before	After	p value#	% change	Before	After	p value#	% change		
TC (mg/dL)	257.51 ± 21.82	161.60 ± 39.59	<0.001	37.24 ↓	262.50 ± 38.72	154.55 ± 35.47	<0.001	41.12 ↓	0.566	0.503
TG (mg/dL)	199.71 ± 80.65	165.61 ± 75.47	0.046	17.07 ↓	198.89 ± 56.03	145.59 ± 64.97	<0.001	26.80 ↓	0.966	0.312
LDL-C (mg/dL)	178.16 ± 20.01	89.11 ± 35.10	<0.001	49.98 ↓	181.57 ± 32.10	85.91 ± 35.45	<0.001	52.68 ↓	0.645	0.749
HDL-C (mg/dL)	39.40 ± 9.56	39.37 ± 11.51	0.990	0.08 ↓	41.14 ± 7.81	40.41 ± 9.11	0.696	1.77 ↓	0.478	0.721

n=number of patients in each group, values are expressed as mean ± SD, before=at baseline, after=after intervention, TC=total cholesterol, TG=triglyceride, LDL-C=low density lipoprotein cholesterol, HDL-C=high density lipoprotein cholesterol, P#=in each group as compared to baseline (paired t-test), P*=inter-group comparison at baseline (unpaired t-test), P** = inter-group comparison after intervention (unpaired t-test)

Discussion

Among many cardiovascular disease risk factors hyperlipidemia is considered as a major risk and ultimately leads to atherosclerosis. Two well-known and widely-used drugs of the lipid lowering group HMG-CoA reductase inhibitors (statins) are atorvastatin and rosuvastatin. The present study was designed to compare anti-thrombogenic effect of atorvastatin and rosuvastatin in patients with hyperlipidemia.

Data of VOYAGER meta-analysis suggested that each rosuvastatin dose is equivalent to 3−3.5 times higher for atorvastatin regarding reduction of LDL-C.[23] This would indicate that 5 mg rosuvastatin is equivalent to 15−20 mg of atorvastatin. Another 12-week study showed that both rosuvastatin (5 mg) and rosuvastatin (10 mg) significantly reduced TC and LDL-C compared with atorvastatin (10 mg) treated patients.[11] But there is no such comparative study regarding anti-thrombotic effect between these two drugs. Statins cause down-regulation of coagulation cascade probably as a result of decreased expression of tissue factor (TF) which serves as cofactor for plasma factor VII. Evidence also indicates that increased thrombomodulin expression on endothelial cell may enhance the activity of protein C anticoagulant pathway leading to reduction of thrombin generation.[10]

The present study has observed the beneficial effects of atorvastatin and rosuvastatin on serum lipid profile. Both of them significantly reduced serum TC, TG and LDL-C level after drug treatment, which was similar to previous research findings.[17,22,24]

It is increasingly recognized that statin therapy not only reduces plasma cholesterol levels, but also affects hematologic parameters in patients with hyperlipidemia, another component of its pleiotropic effects.[20] In the present study platelet count and PT were used as hematologic parameters. Atorvastatin was observed to produce a non-significant ($p=0.463$) reduction of platelet count while rosuvastatin had produced a significant ($p=0.021$) decrease in the levels of platelet count following eight weeks of treatment. However, the two groups did not significantly differ between them ($p=0.187$). Significant prolongation of prothrombin time was observed with both atorvastatin and rosuvastatin ($p<0.0001$ and $p=0.003$ respectively) after intervention, but again inter-group difference was not significant ($p=0.573$). Compiling these observations, it may be suggested that regarding platelet count, rosuvastatin produced better anti-thrombogenic effect compared to that of atorvastatin. But regarding PT, its effects were not significantly different compared to atorvastatin.

In one previous study platelet count showed no significant decrease with either atorvastatin (10 mg) or simvastatin (20 mg), but significant prolongation of PT was observed with both of these drugs ($p<0.01$ and $p<0.001$ respectively).[25] This correlates with the findings of our study. Another study using atorvastatin (10 mg), simvastatin (40 mg) and pravastatin (40 mg) produced similar effects on hematologic parameters.[20] Thus these researches suggest that the statins possess anti-thrombogenic property and this observation correlates well with the present one.

In this trial rosuvastatin was more effective than atorvastatin in reduction of platelet count and were similarly effective in increasing PT in hyperlipidemic patients. When anti-thrombogenic effect was assessed by percentage, rosuvastatin demonstrated a higher percentage of ameliorating changes compared to those of atorvastatin. Both drugs exhibited a similar safety profile. Therefore, rosuvastatin (5 mg) is a better therapeutic option compared to atorvastatin (10 mg) in patients with hyperlipidemia.

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