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A Comparison on Effects of High Dose Rosuvastatin versus High Dose Atorvastatin on Lipid Profile and CRP Level in Patients Undergoing Percutaneous Coronary Intervention: A Randomized Study

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ABSTRACT

Background: Statins are the most common drugs used for reducing low-density lipids (LDL). In addition to their lipid-lowering effects, they have well-documented anti-inflammatory actions. The goal of this study was to compare the effects of high dose atorvastatin and rosuvastatin on lipid profiles and high sensitivity C Reactive Protein (hs-CRP) in patients undergoing percutaneous coronary intervention (PCI).

Methods: The study was done between October 2017 and September 2018 in Semnan Kowsar Hospital. In this randomized trial, 69 patients with atherosclerotic coronary artery disease were randomly assigned 1:1 to receive atorvastatin (80 mg daily) or rosuvastatin (40 mg daily) for 4 months. Levels of hs-CRP and lipid profiles including cholesterol, triglyceride, low-density lipids (LDL), and high-density lipids (HDL) were measured and compared before and after the treatments. Lipid profiles were measured at baseline, 2 months, and 4 months of the treatment.

Results: Sixty patients completed the study. The mean age was 61.1 ± 6.6 years with an excess of males. After 4 months, both drugs could significantly reduce LDL levels, however, the between-group differences were not statistically significant. Rosuvastatin significantly increased HDL levels ($p < 0.05$). In addition, triglyceride levels had a significant reduction in both groups, yet the differences were not significant. Both drugs caused significant reductions in hs-CRP levels ($p < 0.05$). Moreover, the effects of treatments were seen in drug naïve patients as well as patients who were on statins prior to the trial.

Conclusion: Our study indicates that high dose therapies with atorvastatin and rosuvastatin have similar effects on lipid profiles and hs-CRP levels in patients undergoing PCI.

Keywords: Rosuvastatin; Atherosclerosis; Atorvastatin; Lipid profile; hs-CRP

Introduction

Atherosclerotic cardiovascular disease (ASCVD) is usually the leading cause of death in the world. Its prevalence is increasing in the Middle East, India, Central and South America.[1] Westernization and urbanization are often responsible for increased mortality and morbidity of ASCVD. [2]

Hyperlipidemia, hypertension, smoking, and diabetes are well-documented risk factors for formation and progression of atherosclerotic plaques.[3,4] Hyperlipidemia is defined as an increase in total cholesterol levels which may or may not be associated with elevated triglyceride (TG) levels.[5] Notably, management of hyperlipidemia has a pivotal role in prevention of ASCVD.

Morbidity and mortality due to ASCVD are often declined by appropriate and sufficient management of hyperlipidemia. It is known with certainty that a healthy life style affects ASCVD and it should be taken into account for patients with hyperlipidemia. [6,7]

Statins as structural analogs of HMG-CoA (3-hydroxy-3-methylglutaryl-coenzyme) have time-honored positions in treating hyperlipidemia. They are recognized as the most common agents for reducing LDL levels.[8]In addition, they can be used in acute coronary syndromes to reduce the likelihood of plaque ruptures.[9] At present, atorvastatin and rosuvastatin are commonly used in practice. The 2018 guideline of American College of Cardiology (ACC) and American Heart Association (AHA) on the management of cholesterol has recommended the statins in all patients with moderate to high risk for ASCVD develpoment. [10]

During recent years, several investigations have been implemented to compare the efficacy of atorvastatin with rosuvastatin in different clinical settings.[11-13] However, most of present findings are far from conclusion. Besides, limited works have been done to explore the effects of a high dose statin therapy in patients undergoing percutaneous coronary intervention (PCI). PCI is a

preferred method for restoration of blood flow in myocardial infarction and also in refractory chronic coronary artery disease. [14]

Our study was designed to compare effects of rosuvastatin with atorvastatin on lipid profiles and CRP levels in patients undergoing PCI.

Patients and Methods

Study design

This randomized, active-controlled, single-blinded, and single center study was carried out in Kowsar Hospital, Semnan, Iran. Sixty-nine patients aged > 50 requiring PCI were included. The study was done between October 2017 and September 2018. For allocation concealment sealed envelopes with enclosed assignments were used. Random number table was used for randomization of the subjects. Both drugs had similar blister packs in color and shape and kept unnamed. In addition, patients had same schedules of administration. Patients were randomly assigned in a 1:1 ratio to oral atorvastatin 80 mg daily, and oral rosuvastatin 40 mg daily for 4 months. Dose reduction was considered in patients with hepatic impairment. Treatments were not ordered for patients with developing myopathy, renal failure, and those with a 3-fold increase in hepatic transaminase levels. Ethics Committee approved the study (IR.SEMUMS.REC.1395.145) and written informed consent was obtained from patients or by the legal representative prior to trial participation. The clinical trial registry number was IRCT2017080625732N24**.** Participants were excluded if they had liver disorders, hepatitis B, hepatitis C, HIV, infection, inflammatory conditions, auto-immune diseases and acute coronary syndromes (unstable angina and myocardial infarction). Pregnant and lactating women were also excluded from the Trial. For patients who had prior use of statins, fixed doses of atorvastatin or rosuvastatin were considered. Individuals were

discontinued from the study for these reasons: safety, lost to follow-up, and voluntary discontinuation.

PCI protocol

All PCI procedures were performed by interventional cardiologists according to the protocols of Kowsar Hospital. The femoral artery was used for catheterization and everolimus eluting stents were implanted for patients. All subjects were administered intravenous heparin (10,000 U) prior to the stenting procedure. Hydrocortisone was given intravenously 30 minutes before the procedure. All patients took daily aspirin (80 mg) and clopidogrel (75 mg).

Efficacy measurement

Lipid profiles were measured at baseline, month 2, and month 4. A total of 7 mL peripheral blood was taken from patients; 2 mL were kept in EDTA anticoagulant tubes for routine blood tests and the rest were centrifuged for sera collection. Changes in LDL and cholesterol levels from baseline to end of the treatment (month 4) were our primary end points. Changes in TG, HDL, hs-CRP, compliance with drug therapy, and adverse effects of the medications were the secondary end points. Lipid profile was assessed using general biochemical kits (Parsazmun, Tehran, Iran). Hs-CRP was measured using immunoturbidimetry (Parsazmun, Tehran, Iran).

Safety measurement

Physical examinations were done at baseline and then at monthly visits by practitioners. CBC, Blood Urea Nitrogen (BUN), creatinine, Aspartate Aminotransferase (AST), Alanine Aminotransferase (ALT), total bilirubin, and direct bilirubin were checked monthly using general

lab kits (Parsazmun, Tehran, Iran). Patients were monitored weekly for any systemic upset and were asked to call the clinic in case of any problem.

Data analysis

For changes in LDL levels, we calculated sixty-nine patients according to the assumption of 15 % dropout in number of patients with 80 % power at a significance level of 0.05. Student *t* test, x^2 test, and Fisher's exact were used for data analysis. Repeated measures ANOVA were used for changes within the groups. $P < 0.05$ was considered for statistically significant differences. Analyses were performed using SPSS software version 21.0 (Chicago, USA).

Results

Baseline characteristics

Of the 69 patients who were included, 7 patients did not enter the study (2 did not take the medications, 4 withdrew consent, and 1 met the exclusion criteria). A total of 62 patients were investigated. Two patients were lost to follow up and finally 60 participants were observed over the course of 4 months. Participants' flow through is shown in Figure 1. The baseline characteristics of patients are presented in Table 1. The mean age was 61.1 ± 6.9 years with an excess of males (58.3 % vs 41.7 %). No significant differences were seen in baseline characteristics. In addition, there were no significant differences in baseline characteristics between drug naïve patients and patients who were previously on statins.

Lipid profile

As shown in Table 2, atorvastatin decreased total cholesterol levels from 166.5 ± 33.9 (mg/dL) at baseline to 129.1 ± 38.4 (mg/dL) at 4 months ($p < 0.01$). After 4 months, baseline cholesterol levels were reduced from 166.4 ± 47.5 (mg/dL) to 127.3 ± 31.1 (mg/dL) ($p < 0.01$) in rosuvastatin group.

The between-group differences were not statistically significant at 4 months ($p = 0.3$). Both therapies could significantly reduce LDL levels, however, the between group differences failed to reach a significant level ($p = 0.21$). Triglyceride levels had significant reduction in both groups ($p < 0.01$), yet the differences were not significant between two groups ($p = 0.61$). Moreover, both treatments caused a rise in HLD levels. Compared to baseline, it was statistically significant in the rousavastain group (from 42.3 ± 23.8 mg/dL to 47.7 ±17.1 mg/dL, $p < 0.05$). As shown in Table 3 and Table 4, we analyzed participants who were statin naïve and participants who were on statin therapy prior to the investigation. There was a significant improvement in lipid profiles in both groups of patients, however, it was greater in participants with history of statins.

Hs-CRP

As shown in Table 5, both drugs significantly reduced hs-CRP levels after 4 months of treatment ($p < 0.05$). The between group differences were not statistically significant.

Safety

Mild gastrointestinal upset was the most common adverse effect seen in 2 patients (6.6 %) who received atorvastatin and in 1 patient (3.3 %) who was given rosuvastatin. Compared to baseline, no increase was observed in serum creatinine. In both groups, there were elevations in ALT and AST levels albeit within normal range. No patient died and no one was withdrawn due to severe adverse effects.

Discussion

To our knowledge this is the first report in Iranian patients to confirm that a 4-month treatment with high dose atorvastatin and rosuvastatin had equal effects on levels of LDL, total cholesterol, and TG in patients undergoing PCI. In addition, our study showed that rosuvastatin was associated with a greater increase on HDL levels. Besides, both drugs could significantly reduce hs-CRP levels. Statins are almost always the first choices in treating hyperlipidemia. Statins are inhibitors of hepatic HMG-CoA reductase served as a key player in the biosynthesis of VLDL. Statins vary in potency and efficacy. [8,9] Several studies have been implemented to compare the lipid lowering effects of atorvastatin and rosuvastatin. STELLAR trial was one of the first investigations which compared the efficacy of different doses of statins. [15] STELLAR trial demonstrated that rosuvastatin was the most efficacious statin. Of note, in STELLAR trial the anti-inflammatory effects of statins were not evaluated. Furthermore, included subjects had a wide range of age. Nichol's investigation provided a comparative evidence for atorvastatin and rosuvastatin.[16] It was shown that a 104-week treatment with both drugs were effective to improve lipid profile. However, rosuvastatin was associated with lower LDL levels and higher HDL levels. Compared to our work, this trial included a wider range of age accompanying with at least 20% coronary stenosis. Another work by Lee et al showed that 20 mg atorvastatin and 10 mg rousvastatin had similar effects on serum lipids after 6 months of treatment. However, rosuvastatin therapy was linked with a greater decrease in regression of coronary atherosclerosis.[17]A study showed that a 3-month therapy with 10 mg rosuvastain could cause a significant decrease in CRP and matrix metalloproteinase-9 levels. It could also significantly increase adiponectin levels as compared to 10 mg atorvastatin in 69 patients with hypercholesterolemia. [18] In addition, a post hoc analysis by Puri et al, demonstrated that 24-months treatment with high dose rosuvastatin and atorvastatin were effective to reduce LDL and CRP, but over one third of study patients did not have a fall in CRP

as compared to baseline values.[19] Our findings showed that rosuvastatin and atorvastatin are effective to improve lipid profiles and also are able to decrease inflammatory responses. of note, some reports have shown greater responses following rosuvastatin and some have shown an equal efficacy. Statins are usually associated with acceptable safety profiles. Diarrhea, arthralgia, and pharyngitis are reported in 5-10 % of patients. Concomitant use of statins with fibrates like gemfibrozil may lead to an increased risk of myopathy. Of note, niacin and cyclosporine can increase the risk of myopathy. [20]As mentioned, mild gastrointestinal upset was the most common side effect reported in our study. Moreover, Nichol's investigation showed an increase in liver enzymes which was more common in atorvastatin group than rosuvastatin group (2.0% vs. 0.7%).[16]In the present investigation, no serious adverse effects were noted. Compared to published works, there was a relatively long duration of follow-up in our study.

The present study had a number of limitations that should be addressed. It was single center and due to limited number of patients our findings should be confirmed in large multicenter trials with longer time frame. It remains unclear whether long-term use of intensive statin regimens is associated with better therapeutic outcomes. Finally, we were not able to evaluate plaque progression or regression in order to provide a deeper insight about the medical treatments.

CONCLUSION

Our study indicates that high dose atorvastatin and rosuvastatin have similar effects on improving lipid profiles and levels of hs-CRP in patients undergoing PCI. In addition, their effects in drug naïve patients and in patients who had history of statin therapy are similar.

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CONFLICT OF INTEREST

None

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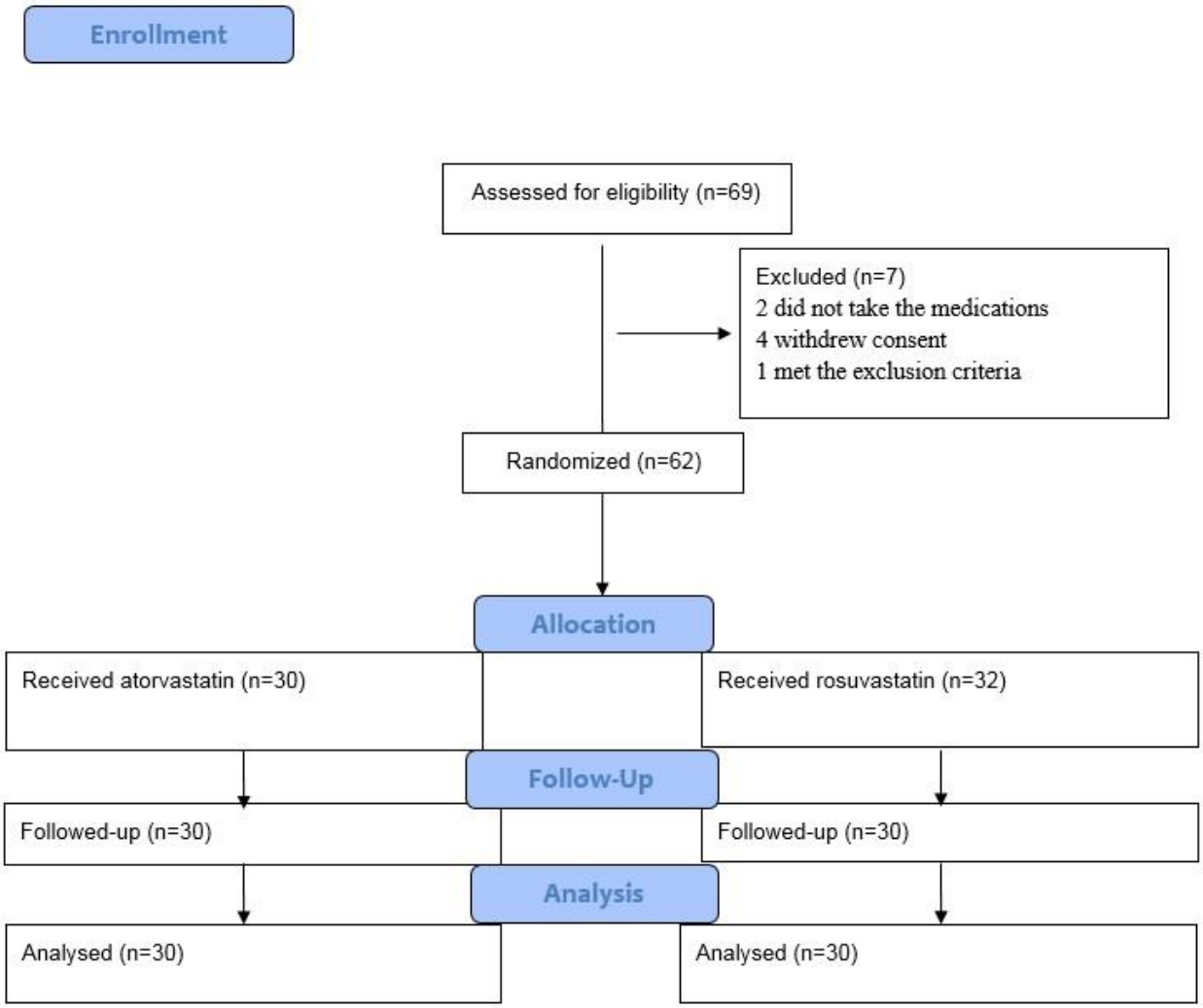

Figure 1. Consort statement of the study

Table 1. Characteristics of all participants at baseline

Characteristics	**Atorvastatin (n=30)**	**Rosuvastatin (n=30)**	**p**
Age, y	60.8 ± 6.5	61.4 ± 6.7	0.41
Age (range)	50-71	50-70	0.32
Female	11 (36.7)	14 (46.7)	0.22
Male	19 (63.3)	16 (53.3)	0.3
Disease			
Diabetes mellitus (DM)	3 (10)	6 (20)	0.81
Hypertension (HTN)	2 (6.8)	1 (3.8)	0.62
coronary artery disease (CAD)	10 (33.3)	10 (33.3)	0.52
CAD+DM	3 (10)	3 (10)	0.22
CAD+HTN	13 (43)	9 (30)	0.3
CAD+HTN+DM	3 (6)	10 (20)	0.3
CAD+HTN+DM+Hyperlipidemia	1(3.3)	2 (6.7)	0.11
Previous antihyperlipidemic drug			
None	5 (16.6)	4 (13.3)	0.3
Atorvastatin	25 (83.3)	26 (86.6)	0.2
Rousvastain	0	0	0.1
LDL, mg/dL	113.2 ± 28.5	111.2 ± 21.1	0.42
HDL, mg/dL	42.4 ± 8.2	42.3 ± 6.8	0.2
TG, mg/dL	172.7 ± 63.1	178.6 ± 69.9	0.37
Total cholesterol, mg/dL	166.5 ± 33.9	166.4 ± 47.5	0.11
Left Ventricular ejection fraction (%)	61.8±3.1	60.7± 25	0.63
Hs-CRP, mg/L	9.8 ± 5.1	10 ± 6.7	0.4
Hemoglobin, g/L	10.5 ± 4.6	10.3 ± 6.6	0.5
Total WBC count, 10^9/L	7.4 ± 3.3	7.9 ± 1.6	0.83

Data are shown as mean ± SD or number (%).

Table 2. The effect of atorvastatin and rosuvastatin on serum lipids in all participants

Variable	Atorvastatin (n=30)	Rosuvastatin (n=30)	p
LDL (mg/dL)			
baseline	113.2 ± 28.5	111.2 ± 21.1	0.09
2 months	84.0 ± 6.9	81.2 ± 9.5	0.1
4 months	66.1 ±7.1*	70.7± 6.6*	0.001
HDL (mg/dL)			
baseline	42.4 ± 18.2	42.3 ± 23.8	0.3
2 months	42.9 ± 11.3	43.9 ± 14.1	0.5
4 months	45.4 ± 17.7	47.7 ± 17.1**	0.05
Total cholesterol (mg/dL)			
baseline	166.5 ± 33.9	166.4 ± 47.5	0.08
2 months	148.2 ± 33.1	133.1 ± 29.9	0.06
4 months	129.1 ± 38.4#	127.3 ± 31.1#	0.01
Triglyceride (mg/dL)			
baseline	172.7 ± 63.1	178.6 ± 69.9	0.1
2 months	148.1 ± 30.0	139.2 ± 41.1	0.2
4 months	123.9 ± 55.1#	133.7 ± 54.4#	0.01

Data are shown in mean ± SD. * $p < 0.001$, ** $p < 0.05$, # $p < 0.01$ vs baseline

Table 3. The effect of atorvastatin and rosuvastatin on serum lipids in statins naïve participants

Variable	Atorvastatin (n=5)	Rosuvastatin (n=4)	p
LDL (mg/dL)			
baseline	114.2 ± 25.5	119.2 ± 21.2	0.09
2 months	84.3 ± 4.9	89.2 ± 8.5	0.06
4 months	69.1 ± 6.1*	79.7 ± 5.6	0.05
HDL (mg/dL)			
baseline	39.4 ± 19.2	41.3 ± 21.5	0.2
2 months	41.9 ± 11.1	41.9 ± 11.1	0.9
4 months	41.4 ± 14.7	42.7 ± 15.6	0.1
Total cholesterol (mg/dL)			
baseline	177.7 ± 33.7	166.6 ± 41.5	0.08
2 months	158.4 ± 36.2	152.1 ± 28.9	0.5
4 months	149.2 ± 34.4*	147.4 ± 29.1	0.05
Triglyceride (mg/dL)			
baseline	171.7 ± 63.1	172.1 ± 60.1	0.08
2 months	158.1 ± 32.0	147.1 ± 38.1	0.7
4 months	151.9 ± 54.1	140.7 ± 44.4*	0.05

Data are shown in mean ± SD. * $p < 0.05$ vs baseline

Table 4. The effect of atorvastatin and rosuvastatin on serum lipids in participants receiving statins prior to the study

Variable	Atorvastatin (n=25)	Rosuvastatin (n=26)	p
LDL (mg/dL)			
baseline	111.2 ± 28.5	118.2 ± 21.1	0.07
2 months	79.0 ± 9.9	81.1 ± 6.5	0.07
4 months	63.1 ± 2.1*	71.7 ± 3.6	0.05
HDL (mg/dL)			
baseline	42.7 ± 19.2	42.4 ± 20.0	0.8
2 months	43.9 ± 13.3	41.2 ± 14.2	0.1
4 months	43.4 ± 17.7	49.1 ± 17.1**	0.01
Total cholesterol (mg/dL)			
baseline	176.5 ± 43.3	167.1 ± 33.5	0.5
2 months	152.2 ± 39.3	135.1 ± 34.9	0.8
4 months	128.1 ± 30.7**	131.3 ± 41.1**	0.01
Triglyceride (mg/dL)			
baseline	170.7 ± 53.1	180.6 ± 79.2	0.5
2 months	146.1 ± 30.0	149.2 ± 31.2	0.06
4 months	121.3 ± 53.1**	130.1 ± 49.9**	0.01

Data are shown in mean ± SD. * $p < 0.05$, ** $p < 0.01$ vs baseline

Table 5. Serum hs-CRP (mg/L) at baseline, and after 4 months of treatment in all participants, statin naïve participants, and participants receiving statins prior to the study

Group (number)	baseline	4 months	p
All participants			
Atorvastatin (30)	9.8 ± 5.1	6.3 ± 2.8*	0.05
Rosuvastatin (30)	10 ± 6.7	5.4 ± 2.3*	0.05
statins naïve participants			
Atorvastatin (5)	9.1 ± 4.2	8.9 ± 2.1	0.09
Rosuvastatin (4)	9.9 ± 3.9	8.3 ± 2.3	0.2
receiving statins prior to the study			
Atorvastatin (25)	7.1 ± 2.9	6.1 ± 2.5	0.3
Rosuvastatin (26)	7.7 ± 2.7	5.9 ± 1.1*	0.05

Data are shown in mean ± SD. * p < 0. 05 vs. baseline