ORIGINAL ARTICLE

Comparison of the effects of high-dose atorvastatin and high-dose rosuvastatin on oxidative stress in patients with acute myocardial infarction: A pilot study

Akut miyokart enfarktüslü hastalarda yüksek doz atorvastatin ile yüksek doz rosuvastatinin oksidatif stres üzerine etkilerinin karşılaştırılması: Bir pilot çalışma

Celal Kilit[1], M.D., Fatma Emel Koçak[2], M.D., Türkan Paşalı Kilit[3], M.D.

[1]Department of Cardiology, Dumlupınar University School of Medicine, Kütahya, Turkey
[2]Department of Medical Biochemistry, Dumlupınar University School of Medicine, Kütahya, Turkey
[3]Department of Internal Medicine, Dumlupınar University School of Medicine, Kütahya, Turkey

ABSTRACT

Objective: Oxidative stress is increased in patients with acute myocardial infarction (AMI). Statins reduce oxidative stress independent of their effect in reducing low-density lipoprotein cholesterol (LDL-C). The aim of the present study was to compare the effects of atorvastatin and rosuvastatin on oxidative status by investigating serum paraoxonase, serum arylesterase, total oxidant status, total antioxidant status (TAS) and oxidative stress index (OSI) in patients with AMI.

Methods: Seventy patients with AMI were randomized into 2 groups; total of 55 patients (19 females, 36 males) aged 32 to 86 years completed the study and were included in the analysis. Patients were treated with 80 mg atorvastatin or 40 mg rosuvastatin for 4 weeks. Lipid parameters and parameters of oxidative status were measured at admission and after 4-week statin treatment.

Results: After 4-week treatment, atorvastatin and rosuvastatin were associated with significant reduction in TAS, OSI, total cholesterol, and LDL-C levels. Serum paraoxonase level was significantly increased in both groups, while high-density lipoprotein cholesterol (HDL-C) level was significantly reduced in atorvastatin group. No statistically significant differences were found between atorvastatin and rosuvastatin in terms of actual difference in oxidative stress parameters.

Conclusion: Atorvastatin and rosuvastatin have similar effects on oxidative status in patients with AMI. Rosuvastatin affected HDL-C level more favorably than atorvastatin.

ÖZET

Amaç: Akut miyokart enfarktüslü (AME) hastalarda oksidatif stres artmıştır. Statinler oksidatif stresi, düşük yoğunluklu lipoprotein kolesterol düşürücü etkilerinden bağımsız olarak azaltırlar. Bu çalışmanın amacı, AME'li hastalarda atorvastatin ve rosuvastatinin oksidatif durumu üzerine olan etkilerini, serum paraoksonaz, serum arilesteraz, toplam oksidan durum ve oksidatif stres indeksini araştırarak karşılaştırmaktır.

Yöntemler: Yetmiş AME'li hasta iki gruba randomize edildi. Çalışmayı tamamlayan 32-86 yaş arası 55 hastanın (19 kadın, 36 erkek) verileri analiz edildi. Hastalar dört hafta boyunca 80 mg atorvastatin veya 40 mg rosuvastatin ile tedavi edildi. Lipit parametreleri ve oksidatif durum parametreleri başvuruda ve dört haftalık statin tedavisi sonrasında ölçüldü.

Bulgular: Dört haftalık tedavi sonrasında atorvastatin ve rosuvastatin, toplam antioksidan durumda, oksidatif stres indeksinde, toplam kolesterol ve düşük yoğunluklu lipoprotein kolesterol düzeylerinde anlamlı azalma ile ilişkili bulundu. Serum paraoksonaz düzeyleri her iki grupta da anlamlı olarak artarken yüksek yoğunluklu lipoprotein kolesterol düzeyi, atorvastatin grubunda anlamlı olarak azaldı. Oksidatif stres parametrelerindeki değişim bakımından atorvastatin ve rosuvastatin arasında istatistiksel olarak anlamlı bir fark saptanmadı.

Sonuç: Akut miyokart enfarktüslü hastalarda oksidatif durum üzerine atorvastatin ve rosuvastatinin benzer etkileri vardır. Rosuvastatin yüksek yoğunluklu lipoprotein kolesterol düzeyini atorvastatine göre daha olumlu etkilemektedir.

Received: August 09, 2016 *Accepted:* January 24, 2017

Correspondence: Dr. Celal Kilit. Zafertepe Mahallesi, Doğal Sokak, Kent Sitesi, No: 7, D: 5, 43020 Kütahya, Turkey.
Tel: +90 274 - 231 66 60 / 4001 e-mail: ckilit@hotmail.com

Oxidative stress is a condition in which reactive oxygen species (ROS) exert toxic effect as result of increased production or altered mechanism of protection.[1] Ischemic and reperfusion injury in acute myocardial infarction (AMI) is a consequence of oxidative stress and may lead to myocardial necrosis. In addition to reperfusion therapies, treatment options to reduce oxidative stress are needed to prevent oxidative stress-related myocardial injury in AMI.

Statins have been shown to reduce the incidence of cardiovascular (CV) events and to reduce all-cause mortality in patients with AMI in multiple large trials. They are highly effective at reducing plasma level of low-density lipoprotein cholesterol (LDL-C) and most statins have modest (about 5%) high-density lipoprotein cholesterol (HDL-C)-raising properties, especially rosuvastatin. Mechanisms of benefit seen with statins are not completely understood and benefits cannot be explained with just effects on lipids. Beneficial effect of statins on CV risk also occurs in persons with normal plasma cholesterol levels due to pleiotropic cholesterol-independent activities of statins. Reduction of oxidative stress is one of the proposed pleiotropic effects of statins. Statins decrease vascular ROS production independent of cholesterol reduction.[2] Not only do statins reduce generation of ROS, but they also inhibit respiratory burst of phagocytes, antagonize pro-oxidant effect of angiotensin II and endothelin-1, and increase synthesis of vascular nitric oxide. Furthermore, some statins and their metabolites have direct free radical scavenging activity.[3] Therefore, all patients with AMI should receive long-term, intensive lipid-lowering therapy with a statin.[4] Studies comparing effects of statins on oxidative stress after AMI are limited. The aim of the present study was to compare effects of atorvastatin and rosuvastatin on oxidative status in patients with AMI treated with primary percutaneous coronary intervention (PCI).

Abbreviations:

AMI	*Acute myocardial infarction*
ARE	*Arylesterase*
CV	*Cardiovascular*
HDL-C	*High-density lipoprotein cholesterol*
LDL-C	*Low-density lipoprotein cholesterol*
MI	*Myocardial infarction*
OSI	*Oxidative stress index*
PON-1	*Serum paraoxonase/arylesterase 1*
PCI	*Percutaneous coronary intervention*
ROS	*Reactive oxygen species*
TAS	*Total antioxidant status*
TOS	*Total oxidant status*

METHODS

Study population

The study was a prospective, randomized, open-label study conducted with 70 patients with AMI. Patients with non-ST-segment elevation AMI and those with ST-segment elevation AMI who received successful primary catheter-based intervention initiated within 12 hours of symptom onset were eligible to join the study. Combination of criteria was required to meet diagnosis of AMI. Detection of increase of high-sensitivity cardiac troponin above 99th percentile of upper reference limit and at least 1 of the following: (1) symptoms of ischemia, (2) new or presumed new significant ST-T wave changes on 12-lead electrocardiogram, or (3) intracoronary thrombus detected on angiography. All patients had type 1 (spontaneous) MI according to universal classification of MI.[5] Exclusion criteria were treatment with statin or any other lipid-lowering agent within prior 6 months, previous side-effects with statin use, uncontrolled diabetes mellitus (glycated hemoglobin >7%), hepatic dysfunction (persistent elevation of aminotransferases in serum >3 times upper normal limit) or severe renal impairment (creatinine clearance <30 mL/minute), acute infectious disease, cardiogenic shock or resuscitation on admission, and homozygote familial hypercholesterolemia. Eligible patients were equally randomized for treatment with atorvastatin (80 mg) or rosuvastatin (40 mg) for 4 weeks (Figure 1). Four-week study period was chosen since in many studies, lipid-lowering, anti-inflammatory and antioxidant effects of statins were observed after 4 weeks of treatment.[6–8] First dose of statin was given immediately after successful primary PCI. Patients were informed about side effects that might occur due to statins and other medications, and were told to contact the physician in event of side effect occurrence. In addition to statin therapy, acetyl salicylic acid, clopidogrel or ticagrelor, anticoagulants, beta-blockers, and angiotensin converting enzyme inhibitors/angiotensin receptor blockers were prescribed for all eligible patients as recommended by recent guidelines.[4] All patients received dietary education from experienced dietician before discharge. Dietary recommendations were as follows: (1) total calories calculated to maintain or attain healthy body weight (body mass index <25 kg/m^2), (2) saturated fat intake limited to maximum of 10% of energy and intake of trans fatty acids limited to maximum 1% of

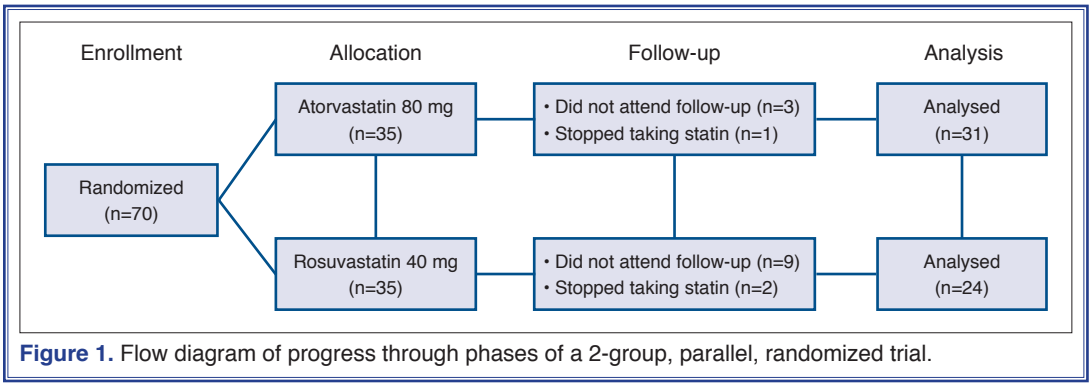

Figure 1. Flow diagram of progress through phases of a 2-group, parallel, randomized trial.

energy, (3) at least 1, preferably 2, portions of oily fish per week, (4) sufficient quantity of fruits and vegetables (≥400 g/day), (5) sufficient fiber-containing grain products, legumes, and/or nuts (≥3 U/day), and (6) salt intake limited to maximum 2400 mg/day. Patients were seen in follow-up 4 weeks after initiation of therapy. Three of the patients in atorvastatin group and 9 patients in rosuvastatin group did not attend follow-up. One of the patients in atorvastatin group and 2 of the patients in rosuvastatin group stopped taking statin for nonpharmacological reasons. In all, 55 patients (19 females, 36 males) aged 32 to 86 years were analyzed at the end of the study. None of the patients who completed the study had side effect or complication related to statin.

The study was performed in accordance with ethical principles set forth in the Declaration of Helsinki and was approved by Dumlupınar University Clinical Research Ethics Committee (December 21, 2015, 2015/16). Written informed consent was obtained from all patients.

Blood sample collection

Venous blood samples were collected in evacuated serum separator clot activator tube (Vacuette Z Serum Sep Clot Activator; GreinerBio-One GmbH, Kremsmunster, Austria) for biochemical analyses and 2.0 mL dipotassium ethylene diamine tetra-acetic acid vacuum tube (BD Vacuteiner; Becton, Dickinson and Company, Franklin Lakes, NJ, USA) for complete blood cell count. Blood samples were centrifuged at 1500 g for 15 minutes within 1 hour of collection to obtain serum samples. Serum samples were aliquoted into polystyrene tubes, and aliquots were stored at -80°C until total antioxidant status (TAS), total oxidant status (TOS), serum paraoxonase/arylesterase 1 (PON-1), and arylesterase (ARE) levels were measured. The investigator executing biochemical analyses was blinded to the randomization.

Measurement of serum total antioxidant status levels

Serum TAS levels were measured using Beckman Coulter AU680 instrument (Beckman Coulter, Inc., Brea, CA, USA) with commercial reagents (Rel Assay Diagnostics, Gaziantep, Turkey). Method was based on novel automated measurement methods developed by Erel.[9] In this method, antioxidant molecules in the sample decolorize 2,2'-azino-bis (3-ethylbenzothiazoline-6-sulfonic acid) cationic radical. Decolorization rate is proportional to quantity of antioxidant molecules present. Trolox (F. Hoffmann-La Roche AG, Basel, Switzerland), a vitamin E analog, was used as calibrator. Results of assay were expressed in terms of millimolar Trolox equivalent per liter (mmol Trolox Eq/L).

Measurement of serum total oxidant status levels

Serum TOS level was measured with Beckman Coulter AU680 instrument and commercial reagents using novel automated measurement methods developed by Erel.[10] Oxidants present in the sample oxidize ferrousion-o-dianisidine complex to ferric ion, and glycerol molecules that are abundantly present in the reaction medium enhance the oxidation reaction. Ferric ion produces a complex colored with xylenol orange in an acidic medium. Color intensity is related to number of oxidant molecules present in the sample. Hydrogen peroxide was used to calibrate the assay and results were expressed in terms of micromolar hydrogen peroxide equivalent per liter (μmol H_2O_2 Eq/L).

Calculation of oxidative stress index

Percent ratio of TOS to TAS was accepted as oxidative stress index (OSI), an indicator of degree of oxidative

stress. To TAS in mmol Trolox equivalent/L was converted to μmol Trolox equivalent/L, after which OSI was calculated as follows: OSI = [(TOS, μmol H_2O_2 Eq/L)/(TAS, μmol Trolox Eq/L) × 100].[11] The results were expressed as arbitrary units.

Measurement of serum paraoxonase-1 and arylesterase activities

Serum PON-1 and ARE activities were measured using Beckman Coulter AU680 instrument and commercial assay reagents. PON-1 activity measurements were performed in the absence (basal activity) and presence of sodium chloride (salt-stimulated activity). Rate of paraoxon hydrolysis (diethyl-p-nitrophenylphosphate) was measured by monitoring increase in absorbance at 412 nm at 37°C. Quantity of generated p-nitrophenol was calculated from molar absorptivity coefficient at pH of 8.5, which was 18,290 M–1 cm–1.[12] Phenylacetate was used as substrate to measure ARE activity. Enzymatic activity was calculated from molar absorptivity coefficient of phenol produced, 1310 M–1 cm–1. One unit of ARE activity was defined as 1 μmol phenol generated/minute under the above conditions.[13] PON-1 and ARE activities were expressed as unit/L.

Measurement of other biochemical parameters

Complete blood cell count was analyzed in whole blood sample, collected in dipotassium ethylene diamine tetra-acetic acid tubes. Blood cell count was analyzed using Beckman Coulter LH 780 Gen-S automated hematology instrument (Beckman Coulter, Inc., Brea, CA, USA) and original reagents. Routine biochemical parameters were measured in the serum samples on day blood was collected, without storage. Serum glucose, creatinine, total cholesterol, HDL-C, LDL-C, triglyceride, and C-reactive protein levels were measured using Beckman Coulter AU680 instrument with original reagents. Non-HDL cholesterol was calculated by subtracting HDL-C from total cholesterol.

Statistical analysis

Normal distributions of continuous variables were evaluated using Kolmogorov-Smirnov test. Results with normal distribution were expressed as mean±SD, while data with non-normal distribution were expressed as median with interquartile range (25^{th}/75^{th} percentiles) for continuous variables. Categorical variables were expressed as percentages. Actual differences were calculated by subtracting baseline values from post-treatment values. Statistical analyses were performed using IBM SPSS Statistics for Windows, Version 22.0 (IBM Corp., Armonk, NY, USA). For continuous variables, differences between 2 groups were compared using Student's t-test for normally distributed data and Mann–Whitney U-test for non-parametric data. Categorical parameters were analyzed with chi-square test. Dependent variables were tested with paired t-test for normally distributed data and Wilcoxon signed rank test for non-parametric data. $P<0.05$ was considered statistically significant for all tests.

RESULTS

There were no significant differences in terms of baseline clinical characteristics or laboratory parameters between the 2 groups (Table 1). Fifty-two percent of the patients in atorvastatin group and 42% of the patients in rosuvastatin group used clopidogrel (p=0.464). Table 2 illustrates comparison of effects of atorvastatin and rosuvastatin on lipid parameters after 4-week treatment. Serum levels of total cholesterol, LDL-C, and non-HDL cholesterol were significantly lower with atorvastatin and rosuvastatin treatment. Actual difference in these cholesterol levels was similar in both groups. HDL-C level was significantly lower in atorvastatin group (p=0.002), and slight increase in rosuvastatin group was not significant (p=0.630). Actual difference in HDL-C level was significantly different (p=0.012). Unlike cholesterol levels, there was no significant change in triglyceride level in either group. TOS and OSI were significantly lower, and PON-1 activity was significantly higher in both groups (Table 3). No statistically significant differences were found between atorvastatin and rosuvastatin in terms of actual difference in TOS, OSI, or PON-1 activity. There was no significant change in TAS or ARE activity in the groups.

DISCUSSION

Oxidative stress is defined circumstances when production of ROS exceeds capacity of endogenous antioxidant systems. Ischemic–reperfusion injury in AMI causes increase in ROS, leading to enhancement of oxidative stress and induction of cardiomyocyte

Table 1. Comparison of clinical characteristics and baseline laboratory parameters of the groups

Variables	Atorvastatin (n=31)	Rosuvastatin (n=24)	*p*
Age (years)	64±11	63±14	0.707
Male gender, n (%)	20 (65)	16 (67)	0.868
Hypertension, n (%)	16 (52)	15 (63)	0.419
Diabetes mellitus, n (%)	8 (26)	5 (21)	0.667
Smoking, n (%)	8 (26)	12 (50)	0.064
ST elevation myocardial infarction, n (%)	19 (61)	9 (38)	0.080
Clopidogrel, n (%)	16 (52)	10 (42)	0.464
Glucose (mg/dL)	142±54	138±45	0.742
Creatinine (mg/dL)	1.05±0.26	0.95±0.21	0.140
Total cholesterol (mg/dL)	213±52	199±44	0.283
Triglyceride (mg/dL)	125 (82/180)	138 (84/288)	0.552
Low density lipoprotein cholesterol (mg/dL)	144±45	128±31	0.132
High density lipoprotein cholesterol (mg/dL)	42±12	40±8	0.378
Non-high density lipoprotein cholesterol (mg/dL)	163±48	165±40	0.745
C-reactive protein (mg/dL)	3.6 (2.5 / 10.9)	3.1 (2.2/6.8)	0.225
Leucocyte ($10^3/\mu L$)	9.89±3.73	9.85±2.18	0.963
Neutrophil ($10^3/\mu L$)	6.88±3.37	6.71±2.24	0.820
Lymphocyte ($10^3/\mu L$)	2.17±1.16	2.32±1.35	0.662
Neutrophil/lymphocyte ratio	2.83 (2.00/5.67)	3.30 (1.41/5.24)	0.418

Values are presented as mean±standard deviation or median with interquartile range (25^{th} / 75^{th} percentiles).

apoptosis/death. In AMI, not only is oxidative stress increased, but antioxidant system, which includes enzymes such as superoxide dismutase and glutathione peroxidase that combat free radicals, is also altered.[14] Furthermore, oxidative stress plays an important role in pathogenesis of major adverse cardiac and cerebrovascular events after primary PCI. Therefore, antioxidative strategies have long been proposed as promising therapy for myocardial damage in AMI patients. Serial changes in antioxidant capacity may serve as predictive marker for CV events after ST elevation MI.[15]

Statin therapy has demonstrated its efficacy in reducing CV mortality in primary and secondary intervention trials.[16] Several studies have shown that statins reduce oxidative stress by decreasing vascular ROS production independent of cholesterol reduction in various patient groups. Sposito et al. demonstrated that timing and potency of statin treatment during AMI are key elements for main mechanisms of benefit.[17] Liang et al. reported that administration of loading-dose rosuvastatin in patients with AMI prior to PCI exerted myocardial protection by inhibiting oxidative stress.[18] These 2 studies showed that anti-inflammatory and antioxidant effects of statins begin in days, and even hours, after AMI. Therefore, we thought that 4-week treatment period was sufficient to compare effects of statins on oxidative status.

An inverse association exists between plasma HDL-C levels and risk for coronary artery disease. HDL-C has antioxidant and anti-inflammatory activities.[19] HDL-C promotes efflux of cholesterol from foam cells, prevents oxidation of LDL-C, and inhibits expression of pro-inflammatory cytokines by macrophages, as well as expression of adhesion molecules by endothelial cells.[20] Antioxidant properties of HDL-C may be due in part to activity of HDL-associated enzymes, such as PON-1. Human serum PON-1 and ARE are both esterase enzymes that have lipophilic antioxidant characteristics, and statin ther-

Table 2. Lipid parameters of the groups after 4-week follow-up

Variables	Baseline	Follow-up	Actual difference	*p**	*p***
Total cholesterol (mg/dL)					
Atorvastatin	213±52	135±38	-78±37	<0.001	0.342
Rosuvastatin	199±44	132±24	-67±44	<0.001	
Triglyceride (mg/dL)					
Atorvastatin	125 (82/180)	133 (102/192)	22 (-45/59)	0.480	0.374
Rosuvastatin	138 (84/288)	134 (98/182)	2 (-52/48)	0.492	
LDL cholesterol (mg/dL)					
Atorvastatin	144±45	68±31	-76±36	<0.001	0.277
Rosuvastatin	128±31	63±22	-65±34	<0.001	
HDL cholesterol (mg/dL)					
Atorvastatin	42±12	37±10	-2 (-10 / 2)	0.002	0.012
Rosuvastatin	40±8	41±9	1 (-4 / 5)	0.630	
Non-HDL cholesterol (mg/dL)					
Atorvastatin	163±48	97±30	-66±36	<0.001	0.087
Rosuvastatin	165±40	82±27	-83±36	<0.001	

Values are presented as mean ± standard deviation or median with interquartile range (25th/75th percentiles).
*Within-group comparison. Paired t-test and Wilcoxon signed rank test were used for statistical analyses.
**Between-group comparison. Student's t-test and Mann–Whitney U-test were used for statistical analyses.
HDL: High density lipoprotein; LDL: Low density lipoprotein.

apy is associated with significant elevation in PON-1 activities.[21]

Rosuvastatin has beneficial effect on oxidative stress in patients with metabolic syndrome.[22] In dyslipidemic patients, atorvastatin treatment increased plasma total antioxidant capacity, decreased level of oxidative stress, and increased PON activity, especially in patients with HDL-C level above 35 mg/dL.[23,24] Lovastatin exerts antioxidant effect in hemodialyzed patients.[25] There might be certain differences in effects of lipophilic and hydrophilic statins and association with oxidative stress levels in AMI patients. Therefore, we investigated oxidative stress status in AMI patients with lipophilic atorvastatin and hydrophilic rosuvastatin. In order to determine oxidative stress, TOS level, which reflects total quantity of ROS in the body, was assessed. By measuring TOS level, numerous oxidative stress products in the serum were determined, such as reactive nitrogen types, hydrochloric acid, malonyldialdehyde, and lipid peroxides.[10] In this study, TAS was used to measure sum of antioxidant molecules. When oxidative products increase dramatically, production of antioxidant protection systems also increases accordingly in order to try and maintain functional integrity. Therefore, separate identification of TAS and TOS levels may be insufficient to reflect stress status. OSI is the most significant parameter used to reflect oxidative stress status. To the best of our knowledge, this is the first clinical trial to compare effects of atorvastatin and rosuvastatin on oxidative stress status in patients with AMI and no difference was noted between atorvastatin and rosuvastatin at the conclusion of 4 weeks. TOS and OSI were similarly reduced with atorvastatin and rosuvastatin, but TAS was not altered in either group.

Another result of our study was finding that atorvastatin and rosuvastatin reduced total cholesterol by similar amount. This result contradicts previous studies.[26,27] On the other hand, after 4-week treatment with atorvastatin, HDL-C level was significantly lower. In a study that compared efficacy of rosuvastatin with that of atorvastatin in decreasing LDL-C in patients with acute coronary syndrome, HDL-C decreased by 1.3% with 80 mg atorvastatin, whereas 8.1% increase was observed with 40 mg rosuvastatin at week 2.[28] At weeks 6 and 12, HDL-C had increased in both groups. These results show that atorvastatin has short-term, reversible HDL-C lowering effect at the beginning of

Table 3. Oxidative stress parameters of the groups after 4-week follow-up

Variables	Baseline	Follow-up	Actual difference	*p**	*p***
TOS, μmol H_2O_2 Eq/L					
Atorvastatin	5.7 (4.0/10.4)	3.0 (2.6/3.6)	-2.9 (-6.0/-1.1)	<0.001	0.375
Rosuvastatin	5.5 (4.2/7.3)	3.3 (2.8/3.7)	-2.3 (-4.4/-0.5)	<0.001	
TAS, mmol Trolox Eq/L					
Atorvastatin	1.54±1.18	1.58±0.27	0.04±0.21	0.342	0.701
Rosuvastatin	1.46±0.18	1.47±0.25	0.01±0.30	0.856	
Serum PON-1, U/L					
Atorvastatin	140 (106/323)	161 (111/372)	16 (1/46)	0.010	0.982
Rosuvastatin	92 (66/303)	112 (91/337)	18 (3/40)	0.005	
Serum ARE, U/L					
Atorvastatin	621±210	680±157	59±206	0.177	0.645
Rosuvastatin	582±131	618±155	36±111	0.122	
OSI, arbitrary unit					
Atorvastatin	0.59±0.60	0.24±0.12	-0.35±0.59	<0.001	0.621
Rosuvastatin	0.52±0.42	0.24±0.08	-0.28±0.40	<0.001	

Values are presented as mean ± standard deviation or median with interquartile range (25^{th}/75^{th} percentiles).
*Within-group comparison. Paired t-test and Wilcoxon signed rank test were used for statistical analyses.
**Between-group comparison. Student's t-test and Mann-Whitney U-test were used for statistical analyses.
ARE: Arylesterase; Eq: Equivalent; OSI: Oxidative stress index; PON-1: Paraoxonase-1; TAS: Total antioxidant status; TOS: Total oxidant status.

treatment. Despite HDL-C reduction with atorvastatin treatment, HDL-linked antioxidant enzyme-PON-1activities increased in both atorvastatin and rosuvastatin groups. PON-1 activity enhancer effect of atorvastatin is independent of alteration in HDL-C level.

ARE activity represents one of the antioxidant enzymatic activities of PON-1 enzyme, which has important role in modulating oxidative stress and in protection from CV disease.[29] In our study, increases in serum ARE activities in atorvastatin and rosuvastatin groups were observed, but did not reach statistical significance.

Positive effect of clopidogrel on endothelial function has been demonstrated in previous studies.[30] However, results of studies investigating effects of clopidogrel on oxidative stress are contradictory.[31,32] Impact of ticagrelor on endothelial function and oxidative stress is unknown, and no study to date has compared the 2 antiaggregant drugs in randomized, blinded fashion. Schnorbus et al. designed a study to test effect of clopidogrel, prasugrel, and ticagrelor on multiple parameters of vascular function, platelet aggregation, oxidative and inflammatory stress before and up to 4 weeks after coronary artery stenting.[33] Result of this study will provide very important information about effects of these antiaggregants on oxidative and inflammatory stress. We believe that, regardless of effects of clopidogrel and ticagrelor on oxidative stress, results of our study would not be affected due to similar rate of use of these 2 antiaggregants in both statin groups.

Limitations

The main limitation of our study is the small number of patients enrolled. Second, evaluation of changes in specific ROS could provide better assessment of effects of statins on oxidative status. Wide age range of study population is another limitation of our study. It would be more appropriate to select patients from similar age groups, as oxidative status may change with age. Finally, changes in inflammatory markers and their relationships with oxidative stress parameters were not evaluated in the present study.

In conclusion, results of our study indicated that atorvastatin and rosuvastatin had similar effect on oxidative status in patients with AMI at 4-week follow-up. They improved activity of PON-1 and reduced TOS similarly. Rosuvastatin affected HDL-C level

more favorably than atorvastatin. Effects of atorvastatin and rosuvastatin on oxidative status seem to be independent of their effects on HDL-C. Further clinical studies with longer follow-up period are needed to expand upon the findings.

Funding sources

None

Conflict-of-interest issues regarding the authorship or article: None declared

REFERENCES

1. Block G, Dietrich M, Norkus EP, Morrow JD, Hudes M, Caan B, et al. Factors associated with oxidative stress in human populations. Am J Epidemiol 2002;156:274–85. [CrossRef]
2. Sumi D, Hayashi T, Thakur NK, Jayachandran M, Asai Y, Kano H, et al. A HMG-CoA reductase inhibitor possesses a potent anti-atherosclerotic effect other than serum lipid lowering effects-the relevance of endothelial nitric oxide synthase and superoxide anion scavenging action. Atherosclerosis 2001;155:347–57. [CrossRef]
3. Beltowski J. Statins and modulation of oxidative stress. Toxicol Mech Methods 2005;15:61–92. [CrossRef]
4. Steg PG, James SK, Atar D, Badano LP, Blömstrom-Lundqvist C, Borger MA, et al. ESC Guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation. Eur Heart J 2012;33:2569–619.
5. Thygesen K, Alpert JS, Jaffe AS, Simoons ML, Chaitman BR, White HD, et al. Third universal definition of myocardial infarction. Eur Heart J 2012;33:2551–67. [CrossRef]
6. Plenge JK, Hernandez TL, Weil KM, Poirier P, Grunwald GK, Marcovina SM, et al. Simvastatin lowers C-reactive protein within 14 days: an effect independent of low-density lipoprotein cholesterol reduction. Circulation 2002;106:1447–52.
7. Landmesser U, Bahlmann F, Mueller M, Spiekermann S, Kirchhoff N, Schulz S, et al. Simvastatin versus ezetimibe: pleiotropic and lipid-lowering effects on endothelial function in humans. Circulation 2005;111:2356–63. [CrossRef]
8. Liu PY, Liu YW, Lin LJ, Chen JH, Liao JK. Evidence for statin pleiotropy in humans: differential effects of statins and ezetimibe on rho-associated coiled-coil containing protein kinase activity, endothelial function, and inflammation. Circulation 2009;119:131–8. [CrossRef]
9. Erel O. A novel automated method to measure total antioxidant response against potent free radical reactions. Clin Biochem 2004;37:112–9. [CrossRef]
10. Erel O. A new automated colorimetric method for measuring total oxidant status. Clin Biochem 2005;38:1103–11. [CrossRef]
11. Akcilar R, Akcilar A, Savran B, Ayada C, Kocak C, Kocak FE, et al. Effects of ukrain in rats with intestinal ischemia and reperfusion. J Surg Res 2015;195:67–73. [CrossRef]
12. Eckerson HW, Wyte CM, La Du BN. The human serum paraoxonase/arylesterase polymorphism. Am J Hum Genet 1983;35:1126–38.
13. Haagen L, Brock A. A new automated method for phenotyping arylesterase (E.C.3·1·1·2) based upon inhibition of enzymatic hydrolysis of 4-nitrophenyl acetate by phenyl acetate. Eur J Clin Chem Clim Biochem 1992;30:391–5.
14. Patil N, Chavan V, Karnik ND. Antioxidant status in patients with acute myocardial infarction. Indian J Clin Biochem 2007;22:45–51. [CrossRef]
15. Abe N, Kashima Y, Izawa A, Motoki H, Ebisawa S, Miyashita Y, et al. A 2-year follow-up of oxidative stress levels in patients with ST-segment elevation myocardial infarction: a subanalysis of the ALPS-AMI study. Angiology 2015;66:271–7.
16. Baigent C, Keech A, Kearney PM, Blackwell L, Buck G, Pollicino C, et al; Cholesterol Treatment Trialists' (CTT) Collaborators. Efficacy and safety of cholesterol-lowering treatment: prospective meta-analysis of data from 90,056 participants in 14 randomized trials of statins. Lancet 2005;366:1267–78.
17. Sposito AC, Santos SN, de Faria EC, Abdalla DS, da Silva LP, Soares AA, et al. Timing and dose of statin therapy define its impact on inflammatory and endothelial responses during myocardial infarction. Arterioscler Thromb Vasc Biol 2011;31:1240–6. [CrossRef]
18. Liang D, Zhang Q, Yang H, Zhang R, Yan W, Gao H, et al. Anti-oxidative stress effect of loading-dose rosuvastatin prior to percutaneous coronary intervention in patients with acute coronary syndrome: a prospective randomized controlled clinical trial. Clin Drug Investig 2014;34:773–81. [CrossRef]
19. Barter P, Kastelein J, Nunn A, Hobbs R. High density lipoproteins (HDLs) and atherosclerosis: the unanswered questions. Atherosclerosis 2003;168:195–211. [CrossRef]
20. Barter PJ, Baker PW, Rye KA. Effect of high-density lipoproteins on the expression of adhesion molecules in endothelial cells. Current Opinion in Lipidology 2002;13:285–8. [CrossRef]
21. Ferretti G, Bacchetti T, Sahebkar A. Effect of statin therapy on paraoxonase-1 status: A systematic review and meta-analysis of 25 clinical trials. Prog Lipid Res 2015;60:50–73. [CrossRef]
22. Bostan C, Yildiz A, Ozkan AA, Uzunhasan I, Kaya A, Yigit Z. Beneficial effects of rosuvastatin treatment in patients with metabolic syndrome. Angiology 2015;66:122–7. [CrossRef]
23. Uydu HA, Yıldırmış S, Orem C, Calapoglu M, Alver A, Kural B, et al. The effects of atorvastatin therapy on rheological characteristics of erythrocyte membrane, serum lipid profile and oxidative status in patients with dyslipidemia. J Membr Biol 2012;245:697–705. [CrossRef]
24. Kural BV, Orem C, Uydu HA, Alver A, Orem A. The effects of lipid-lowering therapy on paraoxonase activities and their relationships with the oxidant-antioxidant system in patients with dyslipidemia. Coron Artery Dis 2004;15:277–83.
25. Mastalerz-Migas A, Reksa D, Pokorski M, Steciwko A, Muszyńska A, Bunio A, et al. Comparison of a statin vs. hypolipemic diet on the oxidant status in hemodialyzed patients

with chronic renal failure. J Physiol Pharmacol 2007;58 Suppl 5(Pt 1):363–70.

26. Jones PH, Davidson MH, Stein EA, Bays HE, McKenney JM, Miller E, et al. STELLAR Study Group. Comparison of the efficacy and safety of rosuvastatin versus atorvastatin, simvastatin, and pravastatin across doses (STELLAR* Trial). Am J Cardiol 2003;92:152–60. [CrossRef]
27. Rosenson RS. Rosuvastatin: a new inhibitor of HMG-coA reductase for the treatment of dyslipidemia. Expert Rev Cardiovasc Ther 2003;1:495–505. [CrossRef]
28. Pitt B, Loscalzo J, Monyak J, Miller E, Raichlen J. Comparison of lipid-modifying efficacy of rosuvastatin versus atorvastatin in patients with acute coronary syndrome (from the LUNAR study). Am J Cardiol 2012;109:1239–46. [CrossRef]
29. Eom SY, Kim YS, Lee CJ, Lee CH, Kim YD, Kim H. Effects of intronic and exonic polymorphisms of paraoxonase 1 (PON1) gene on serum PON1 activity in a Korean population. J Korean Med Sci 2011;26:720–5. [CrossRef]
30. Warnholtz A, Ostad MA, Velich N, Trautmann C, Schinzel R, Walter U, et al. A single loading dose of clopidogrel causes dose-dependent improvement of endothelial dysfunction in patients with stable coronary artery disease: results of a double-blind, randomized study. Atherosclerosis 2008;196:689–95. [CrossRef]
31. Taher MA, Nassir ES. Beneficial effects of clopidogrel on glycemic indices and oxidative stress in patients with type 2 diabetes. Saudi Pharm J 2011;19:107–13. [CrossRef]
32. Ramadan R, Dhawan SS, Syed H, Pohlel FK, Binongo JN, Ghazzal ZB, et al. Effects of clopidogrel therapy on oxidative stress, inflammation, vascular function, and progenitor cells in stable coronary artery disease. J Cardiovasc Pharmacol 2014;63:369–74. [CrossRef]
33. Schnorbus B, Daiber A, Jurk K, Warnke S, König J, Krahn U, et al. Effects of clopidogrel, prasugrel and ticagrelor on endothelial function, inflammatory and oxidative stress parameters and platelet function in patients undergoing coronary artery stenting for an acute coronary syndrome. A randomised, prospective, controlled study. BMJ Open 2014;4:e005268.

Keywords: Acute myocardial infarction; arylesterase; oxidative stress; paraoxonase; statin.

Anahtar sözcükler: Akut miyokart enfarktüsü; arilesteraz; oksidatif stres; paraoksanaz; statin.