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The effect of statin treatment on the prevention of stent mediated flow limited edge dissections during PCI in patients with stable angina

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ABSTRACT

Objectives: The effect of statin therapy before PCI with direct stenting may reduce the development of flow limited edge dissections (ED) in patients with stable angina.
Background: Flow limited ED after PCI is associated with an increased risk of major adverse cardiovascular events. Statin therapy induces important changes in the plaque composition which have been previously identified as strong predictors of ED.
Material and methods: 100 patients complicated with flow limited ED and 100 control patients with successful procedure were enrolled into the study. EDs were described as the 5-mm regions that were immediately adjacent to the stent borders, both distally and proximally on the coronary angiography.
Results: Rate of statin use and duration of statin use were significantly higher in patients with non-ED group (63%) versus ED group (25%) ($p < 0.001$). In addition, patients in ED group had significantly higher levels of C-reactive protein (CRP) at admission (9.9 mg/dL (5.89–16.45) vs. 4.40 mg/dL (3.5–7.09), respectively, $p = 0.014$).
Conclusions: Our findings suggested that maintenance statin treatment before PCI with direct stenting may reduce the development of flow limited ED in patients with stable angina.

1. Introduction

Stenting is the standard technique for the percutaneous treatment of severe coronary artery stenosis [1]. Stent implantation can lead vessel damage including dissections at the stent edges [2,3]. Edge dissections (ED) were defined as the 5-mm regions that were immediately adjacent to the stent borders, both distally and proximally [4]. Procedural such as incomplete lesion coverage and plaque characteristics may be associated with increased risk of ED [5–7]. Plaque morphology, calcium deposit, fibrous cap (FC) thickness over lipid-rich plaques, and vessel overstretching by the stent were independent predictors for the development of ED [4]. There is no increased risk in non-flow limited EDs but flow limited EDs are related with an increased risk of major adverse cardiovascular events (MACE) [8,9]. Flow-limiting EDs are easily identified on angiography and treated with additional stent implantation.

Statins contribute to plaque stabilization by their lipid lowering and pleiotropic effects. Statin therapy can alter the plaque composition with a decrement in the lipid volume and an increment in FC thickness [10,11]. Pleiotropic effects of statins consist of anti-inflammatory properties including significant reductions in C-reactive protein (CRP) levels and stabilization of atherosclerotic plaque [12–16].

The aim of the current study was to investigate the effect of statin on prevention of flow limited EDs in patients who underwent elective coronary angiography and direct stenting due to symptomatic coronary artery disease (CAD).

2. Material and methods

2.1. Study population

A total of 200 patients were selected in a retrospective manner from patients who admitted to Department of Cardiology of Turkiye Yuksek Ihtisas Training and Research Hospital due to symptomatic CAD between January 2009 and December 2013. Elective coronary angiography and direct stenting was performed to all patients because of stable angina pectoris owing to clinical indications, including symptoms of angina and abnormal stress test results, by either exercise treadmill tests or myocardial perfusion scintigraphy.100 patients complicated with flow limited ED and 100 control patients with successful procedure were enrolled into the study.

The study was conducted in agreement with the Helsinki-II-declaration and approved by the ethics committee of the Yuksek Ihtisas Training and Research Hospital. Written informed consent was taken from the patients themselves in life and first-degree relatives of patients who died. Data collection regarding clinical, demographic and laboratory characteristics of patients and in hospital events were conducted on the basis of a review of medical records. Diabetes mellitus was defined as a previous using anti-diabetic drugs or fasting blood glucose >126 mg/dL. Patients using antihypertensive drugs or blood pressure measurements >140/90 mm/HG after 2 consecutive measurement were defined as hypertension.

Exclusion criteria were presence of balloon angioplasty procedure, acute coronary syndrome, end stage renal disease, systemic inflammatory disease, active infections,

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virus related chronic hepatitis, hepatobiliary disease, congestive heart failure and missing or unavailable CRP values. Dissections that occurred after pre-dilation or post-dilation were excluded. Type A and B National Heart, Lung and Blood Institute (NHLBI) coronary minor dissections after direct stenting were accepted as non-flow limited ED and they were excluded from the study.

2.2. PCI procedures

All of PCI procedures were performed with femoral approach according to standard techniques. All patients received a 70 IU/kg intravenous bolus of unfractionated heparin, 300 mg clopidogrel and 300 mg acetylsalicylic acid. Glycoprotein IIb/IIIa inhibitors were administered according to operator preference. Direct stenting with BMS or DES was left to the discretion of the interventional cardiologist according to patient need. Stents were implanted according to current clinical practice. Coronary stenting were performed, and stent size and length selected to fully cover the diseased segment with adequate stent expansion. Procedural success was defined as a final angiographic residual narrowing of 20% by visual estimation. A new stenosis was a new narrowing without adjacent dissection that persisted after the administration of intracoronary nitroglycerin. Dissections were interpreted by experienced interventional cardiologists with angiography. The occurrence of coronary arterial ED during index PCI was defined using National Heart, Lung and Blood Institute (NHLBI) classification and EDs were recorded. Type A and B NHLBI minor dissections were accepted as non-flow limited EDs and they were excluded from the study. Flow limited EDs were defined as type C, D, and E coronary major dissections after direct stenting using (NHLBI) classification system. Flow-limited EDs were treated additional stenting by covering whole of dissection area, successfully. After PCI, all patients were admitted to the coronary care unit; 100 mg aspirin 75 mg clopidogrel, and statins were continued in all patients.

2.3. Laboratory measurements

Laboratory parameters including C-reactive protein and fasting serum levels of glucose, total cholesterol, triglyceride, low-density lipoprotein cholesterol (LDL-C) and high-density lipoprotein cholesterol (HDL-C) were measured using standard enzymatic methods. Transthoracic echocardiography was performed for each patient immediately after PCI in intensive cardiac care unit. All measurements were performed using a commercially available machine (Vivid 7 GE Medical System, Horten, Norway) with a 3.5-MHz transducer.

2.4. Statistical analysis

All statistical studies were carried out using the SPSS program (version 15.0; SPSS, Chicago, Illinois, USA). As the result of post-hoc power calculation using link of http://clincalc.com/Stats/Power.aspx, the power of our study was %90 ($\alpha = 0.5$ and $\beta = 0.1$). Distribution properties of the data were performed using the Kolmogorov–Smirnov test. As mean ± standard deviation for normally distributed data, median (interquartile range) was given for non-normally distributed data. Comparisons of continuous values between two groups were performed by Independent-Samples T test. Comparisons of non-parametric values between the two groups were performed by Mann–Whitney U test. Categorical variables were compared using the Chi-square test or Fisher's exact test. Results were shown as a percent. We performed logistic regression analysis with ED as the dependent variable. The variables that were statistically significant according to the univariate analysis were included in the final multivariate model to identify the ED predictors. Multivariate logistic regression analysis, which included variables with a p value <0.1, was carried out to identify independent predictors of ED. A p value <0.05 was considered statistically significant. The goodness of fit of the model was evaluated by the Hosmer-Lemeshow test.

3. Results

Baseline demographic and clinical characteristics of study patients with and without ED are showed in Table 1. Rate of statin use and duration of statin use were significantly higher in patients with non-ED group versus ED group while other variables between groups were not statistically different. In subgroup analysis according to type of statin therapy, both groups had similar rate of atorvastatin or rosuvastatin therapy (85%(48 patients) in non-ED group versus 84%(21 patients) in ED group.

Baseline laboratory characteristics of the patients are summarized in Table 2. Laboratory characteristics between the two groups were not statistically different including lipid profile. But patients in ED group had significantly higher levels of CRP at admission (Fig. 1) (9.9 mg/dL (5.89–16.45) vs. 4.40 mg/dL (3.5–7.09), respectively, p = 0.014). Additionally, as shown in Fig. 2, CRP levels were also higher in patients who did not use statin compared to patients on statin therapy (9.9 mg/dL (4.6–18) vs. 4.2 mg/dL (3.1–7.9), respectively, p = 0.026). Furthermore, according to subgroup analysis, on-ED group had significantly higher rate of patients with LDL < 70 mg/dL compared to ED group(25(25%) versus 15(15%), respectively, p = 0.001).

Table 1
The baseline demographic and clinical characteristics of groups.

Variables	Non-ED group	ED group	p value
Age (years)	59.2 ± 10.2	58.6 ± 10.2	0.659
Male no. (%)	70 (70%)	80 (80%)	0.140
Smoking, no. (%)	38 (38%)	49 (49%)	0.118
Hypertension, no. (%)	58 (58%)	57 (57%)	0.887
Diabetes mellitus, no.(%)	31 (31%)	32 (32%)	0.879
Prior myocardial infarction, no. (%)	24 (33%)	33 (33%)	0.204
Body mass index (kg/m^2)	29.1 ± 5.7	27.7 ± 4.4	0.327
Systolic blood pressure (mmHg)	129 ± 17	125 ± 21	0.450
Diastolic blood pressure (mmHg)	79 ± 9	78 ± 10	0.701
Left ventricular ejection fraction (%)	55 ± 3	58 ± 5	0.301
Previous medications			
Aspirin, no. (%)	45 (45%)	57 (57%)	0.090
Beta blocker	49 (49%)	50 (50%)	0.888
Angiotensin converting enzyme inhibitor/angiotensin receptor blocker, no. (%)	56 (56%)	57 (57%)	0,887
Calcium channel blocker, no. (%)	5 (%)	6 (%)	0.757
Nitrate, no. (%)	10 (10%)	18 (18%)	0.104
Rosuvastatin	18	4	0.002
Atorvastatin	45	21	<0.001
Statin, no. (%)	63(63%)	25(25%)	<0,001
Duration of statin use, month	21 (0–48)	0 (0–4.5)	<0.001

Peri-procedural intervention and angiographic findings of study groups are showed in Table 3. Patients in ED group had significantly higher total number of stents and more severe stenosis before percutaneous coronary intervention. During hospitalization, acute stent thrombosis was occurred in 12 patients in ED group while there was no any patient with stent thrombosis in non-ED group (p < 0.001). Other variables between the two groups were not statistically different.

After including variables found significant in univariate analysis, the statin use (p < 0.001), duration of statin use for each 1 month (p < 0.001) and LDL < 70 mg/dL (p = 0.01) were found as independent associates of flow limited ED in multivariate regression analysis (Table 4). Additionally, each 1 U/L increase in CRP levels was associated with 2.31-fold risk of flow limited ED (p < 0.001). Hosmer-Lemeshow test showed that the model fit the data well (p = 0.84).

4. Discussion

To the our knowledge, this is the first study that evaluates the effect of statin treatment on flow limited ED in patients undergoing elective PCI for stable angina pectoris. Our study suggested that maintenance statin treatment prior to PCI was associated with reduction of flow limited ED development. Second, The CRP on admission was significantly higher in the non-statin use group and a high level of CRP, indicating increased inflammatory response, was strongly associated with development of flow limited edge dissection.

Table 2
Baseline laboratory measurements of study groups.

Variables	Non-ED group	ED group	p value
Glucose (mg/dL)	130.02(66–498)	128.54(70–420)	0.879
Hemoglobin (g/dL)	13.32 ± 1.75	13.69 ± 1.78	0.141
White blood cell (×10^3/μL)	8.04 ± 2.15	8.45 ± 2.33	0.195
Platelet count (×10^3/μL)	264 ± 74	260 ± 61	0.531
Mean platelet volume (fL)	8.70 ± 0.85	8.63 ± 0.78	0.667
Creatinine (mg/dL)	1.11 ± 0.90	1.01 ± 0.38	0.343
Total cholesterol (mg/dL)	176 ± 43	173 ± 45	0.571
Low density lipoprotein cholesterol (mg/dL)	104 ± 33	108 ± 48	0.470
High density lipoprotein cholesterol (mg/dL)	38 ± 9	40 ± 9	0.296
Triglyceride (mg/dL)	176 (30–654)	154 (40–637)	0.145