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Comparing the Effect of a Preprocedural Loading Dose of Atorvastatin vs. Rosuvastatin on the Prevalence of No-reflow and Low TIMI Flow in Patients with ST-Elevation Myocardial Infarction Undergoing Primary Percutaneous Intervention

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Abstract

Background: As a promising revascularization therapy, percutaneous coronary intervention (PCI) is widely used in patients with coronary artery disease. No-reflow and low thrombolysis in myocardial infarction (TIMI) flow are two adverse periprocedural events.
Objectives: This study aimed to compare the effectiveness of atorvastatin and rosuvastatin in reducing the no-reflow phenomenon in patients undergoing primary PCI.
Methods: Following a randomized control design, 280 eligible patients with no history of MI or ischemic heart disease (IHD) with ST-elevation myocardial infarction (STEMI) who were candidates for coronary angioplasty underwent angioplasty from May 2020 to December 2020.
Results: Our results showed that TIMI flow III was significantly higher in the rosuvastatin group, while the no-reflow was not seen in this group ($P < 0.001$). Also, ST resolution after 90 minutes of PCI was significantly better in the rosuvastatin group.
Conclusions: This study demonstrated that using a loading dose of rosuvastatin could reduce the no-reflow phenomenon in patients undergoing primary PCI.

Keywords: Atorvastatin, Rosuvastatin, No-reflow, Angiography

1. Background

Ischemic heart disease (IHD) is a common disorder with high morbidity and mortality worldwide. Globally, 30% of those suffering from IDH lose their lives (1). Currently, prevention is the primary way to reduce the burden of IHD. Despite using several preventive methods, many patients who suffer from coronary artery disease (CAD) need to undergo percutaneous coronary artery intervention (PCI) still (2). PCI, also called coronary angioplasty, is an invasive therapeutic procedure. While bringing several advantages, it also has rare but significant complications. The periprocedural rise in cardiac enzymes is observed in 48% of patients (3). In addition, traumatic coronary dissection, air embolization, iatrogenic coronary thrombosis, coronary perforation, no-reflow, side branch occlusion, and low thrombolysis in myocardial infarction (TIMI) flow can occur in this invasive procedure (4). Damage to the blood vessel wall during angiography and stent implantation can cause platelet activation and thrombus formation, leading to obstruction (5) that can reverse the revascularization (PCI) outcome. Hence, reducing the incidence of no-reflow after cardiac catheterization is a fundamental challenge for cardiologists.

In recent years, many studies suggested new and low-risk ways to reduce short-term and long-term complications of PCI, including using a new generation of drug stents and balloons while doing the procedure. Statins, such as atorvastatin and rosuvastatin, also have been successfully used to reduce these complications, i.e., by inhibiting 3-hydroxyl-3-methylglutaryl- coenzyme A (HMG-CoA) reductase, which leads to reduced low-density lipoprotein (LDL) in plasma. Furthermore, statins not only prevent inflammation, platelet aggregation, and smooth muscle cell proliferation but also have plaque-stabilizer activity (6). Previous trials demonstrated useful effects of pretreatment with a loading dose of statins in patients with

ST-elevation myocardial infarction (STEMI) undergoing PCI (7-9). In this study, we evaluated and compared the effect of a pre-procedural loading dose of atorvastatin vs. rosuvastatin on the prevalence of no-reflow and low TIMI flow in patients with ST-elevation myocardial infarction undergoing primary percutaneous intervention.

2. Objectives

This study aimed to compare the effectiveness of atorvastatin and rosuvastatin in reducing the no-reflow phenomenon in patients undergoing primary PCI.

3. Methods

3.1. Study Design and Oversight

This randomized control trial was done after getting an approval license from the ethical committee of our university from May 2020 to December 2020. After evaluation against the inclusion criteria, 280 eligible patients with no history of MI or IHD with STEMI who were candidates for coronary angioplasty underwent angioplasty from May 2020 to December 2020. Patients were randomly divided into two groups of atorvastatin (group 1), who received 80 milligrams of atorvastatin loading, and rosuvastatin (group 2), who received 40 mg rosuvastatin loading in the emergency room before the procedure (PCI). The same brand of atorvastatin or rosuvastatin was used for all patients. To reduce the effect of total ischemic time on the no-reflow phenomenon, only patients whose chest pain started 6 hours before PCI were included in this study. All angiography and PCI procedures were done by the same interventional cardiologist to eliminate technical differences effect on no-reflow among patients. Supraflex stent was used for all patients. Only patients who needed one direct stenting were included in this study. Demographic and lab data of all participants were recorded. Patients were reassured that their information would remain confidential. The correspondent interventional cardiologist measured the prevalence of no-reflow and low TIMI flow during coronary angioplasty.

3.2. Participants (Study Population)

Patients aged 18 years or older with STEMI who had chest pain for less than 6 hours were included in this study. ST-elevation myocardial infarction was defined according to the European Society of Cardiology guidelines as 1 mm elevation in 2 adjacent pericardial leads except for V2 and V3 and 2 mm elevation in V2 and V3 leads in patient's electrocardiography. The exclusion criteria were past medical history of inflammatory, renal insufficiency, collagen vascular diseases, and previous myocardial infarction or IHD. In addition, patients with previous use of statins, active infection, blood disorders, and complications of MI, such as pulmonary edema, were excluded from the study.

3.3. Percutaneous Coronary Intervention

The coronary angiography was performed using the standard techniques. Initially, patients were asked to lay on an X-ray table in the supine position. Under cardiac monitoring and pulse-oximetry and after local anesthesia with lidocaine, a small incision was made in the skin near the groin. The catheter was inserted into the femoral artery and then carefully guided to the examined area. Afterward, the contrast agent was injected through the catheter, and a series of X-rays were taken when the contrast flowed through the blood vessel. Then, the site of stenosis in the coronary artery was evaluated.

3.4. Clinical Outcomes and Statistical Analysis

The primary endpoints were the incidence of no-reflow and low TIMI flow after PCI in patients with STEMI receiving loading doses of atorvastatin and rosuvastatin before the procedure. No-reflow is a situation in which blood supply to the myocardium is insufficient because of obstruction in one of the coronary arteries feeding the myocardium. The TIMI flow grade was defined in the first decades of the 1980s to evaluate the quality of coronary artery reperfusion (4).

TIMI flow grading is as follows:

Grade 0: complete obstruction of the coronary artery that leads to no perfusion;

Grade 1: penetration with no perfusion that leads to an incomplete filling of the distal coronary bed;

Grade 2: partial perfusion that leads to delayed filling of the distal portion of the coronary bed;

Grade 3: normal perfusion with the same speed blood flow before and after obstruction (10, 11).

4. Results

A total of 178 patients were included in this study; for 12 patients, PCI was done with non-Supraflex stents because it was not available temporary; for 14 patients, more than one stent was used; and for 16 patients, direct stenting was not possible; hence, they were excluded from the study. Data of 136 patients, with a mean age of 56.2 ± 10.7 years, were included in the final statistical analysis. There was no significant difference between the atorvastatin and rosuvastatin groups concerning atherosclerosis risk factors, except for the peripheral artery disease, which was observed in 4.3%

of patients who received rosuvastatin (Table 1). According to the laboratory data, HDL was the only factor that was significantly higher in the atorvastatin group, and there was no significant difference between the study groups concerning other factors (Table 2). Our results showed that TIMI flow III was significantly higher in the rosuvastatin group, while no-reflow was not seen in this group ($P < 0.001$). Also, ST resolusion after 90 minutes of PCI in the rosuvastatin group was significantly better in the rosuvastatin group (Table 3).

Table 1. Characteristics of the Patients Enrolled in the Two Groups [a]

	Atorvastatin	Rosuvastatin	P-Value
Female gender	56 (40.0)	52 (37.1)	0.623
Age (y)	57.01 ± 10.99	55.79 ± 10.46	0.339
Body mass index (kg/m^2)	26.99 ± 1.53	26.92 ± 1.58	0.736
Current smoker	82 (58.6)	74 (52.9)	0.336
Family history of CAD	40 (28.6)	38 (27.1)	0.790
Hypertension	74 (52.9)	86 (61.4)	0.147
Diabetes mellitus	42 (30.0)	41 (29.3)	1.00
Hypercholesterolemia (%)	55 (39.3)	56 (40.0)	0.982
Renal disease	8 (5.7)	12 (8.6)	0.353
Stroke	12 (8.6 %)	14 (10.0)	0.680
Peripheral arterial disease	0 (0.0)	4 (2.9)	0.044
PCI	26 (18.6)	18 (12.9)	0.189
History of coronary arteries bypass	4 (2.9)	6 (4.3)	0.520

Abbreviation: CAD, coronary artery disease
[a] Values are expressed as No. (%) or mean ± SD.

Table 2. Laboratory Finding of Two Groups of Patients Before Procedure [a]

	Atorvastatin	Rosuvastatin	P-Value
Creatinine (mg/dL)	1.01 ± 0.21	1.04 ± 0.20	0.202
FBS (mg/dL)	109.12 ± 29.92	106.69 ± 30.92	0.504
HbA1C (%)	6.72 ± 0.89	6.83 ± 0.78	0.278
Total cholesterol (mg/dL)	203.64 ± 21.00	207.00 ± 27.93	0.257
Triglyceride (mg/dL)	187.50 ± 24.94	184.04 ± 34.57	0.338
LDL-C (mg/dL)	126.93 ± 9.90	143.24 ± 146.38	0.189
HDL (mg/dL)	35.83 ± 3.68	33.76 ± 2.56	< 0.001

Abbreviations: FBS, fasting blood sugar; HbA1C, hemoglobin A1C; LDL, low-density lipoprotein; HDL, high-density lipoprotein; ECG, electrocardiography
[a] Values are expressed as mean ± SD.

Table 3. Echocardiography, Electrocardiography and Angiography Finding of Two Groups of Patients [a]

	Atorvastatin	Rosuvastatin	P-Value
Left ventricular ejection fraction (%)	32.82 ± 6.66	34.29 ± 6.94	0.073
Number of involved vessels			0.159
1	60 (42.9)	76 (54.3)	
2	72 (51.4)	58 (41.4)	
3	8 (5.7)	6 (4.3)	
Target vessel			0.947
LAD	70 (50.0)	72 (51.4)	
LCX	26 (18.6)	24 (17.1)	
RCA	44 (31.4)	44 (31.4)	
Flow status			< 0.001
No-reflow	72 (51.4)	0 (0.0)	
TIMI III	40 (28.6)	122 (87.1)	
TIMI I, II	28 (20.0)	18 (12.9)	
ST resolusion after PCI			< 0.001
> 50%	58 (41.4)	84 (60.0)	
< 50%	82 (58.6)	56 (40.0)	
Stent diameter (mm)	3.07 ± 0.28	3.15 ± 0.35	0.035
Stent length (mm)	25.06 ± 4.43	23.76 ± 4.75	0.018
Onset of chest pain until PCI (h)	5.47 ± 1.57	5.19 ± 1.76	0.153

[a] Values are expressed as No. (%) or mean ± SD.

5. Discussion

This study demonstrated that rosuvastatin treatment before PCI could improve the outcome according to TIMI flow of infarct-related artery at the end of angioplasty and ST resolution achieved 90 minutes after PPCI. As a promising revascularization therapy, PCI is widely used in patients with CAD (9). Despite extensive efforts to achieve acceptable results, some cases experience inverse outcomes after receiving the procedure. No-reflow and low TIMI flow are two adverse periprocedural events.

In recent years, several studies suggested various ways to prevent such events. The efficacy of loading a dose statin regimes on post-PCI outcomes (the incidence of no-reflow and low TIMI flow) has been studied since 2007, when Patti et al. cited in Kim et al., in an ARMYDA-ACS trial, demonstrated the beneficial effect of atorvastatin pretreatment in patients with ACS undergoing PCI for the first time (7). Liu et al. showed that high-dose atorvastatin could significantly improve the no-reflow phenomenon in patients with STEMI when prescribed before PCI (12).

A meta-analysis of seven studies comprising 3,086 pa-

tients, reported that high-intensity statin administrated before PCI could reduce the no-reflow phenomenon by 4.2%, and this effect was statistically significant (P = 0.016) (13). This study suggested that high-intensity statin should be used before PCI, particularly in STEMI patients. Garcia-Mendez et al., by studying 103 patients with STEMI, showed that atorvastatin 80 mg before PCI could reduce the rate of no-reflow from 63% to 27%, which was statistically significant (14). Previous studies showed that similar doses of rosuvastatin could reduce LDL better than atorvastatin (15). One recent study showed that the long-term outcome of rosuvastatin in post PCI patients was not better than atorvastatin. In this study, in comparison to patients who received atorvastatin 80 mg per day, those on rosuvastatin 40 mg per day showed higher rates of hs-CRP adverse effects, such as gastritis (1).

On the other hand, Aydin et al. reported that high dose atorvastatin and moderate dose rosuvastatin didn't have significant differences regarding LDL-c, hs-CRP, and inflammatory markers in post-MI patients (16). Kim et al. showed that, compared to the control group, patients who took rosuvasttatin 40 mg before primary PCI had reduced infarct size in ingle-photon emission computed tomography (SPECT) imaging 3 days after myocardial infarction (7). Another study showed that patients with ST-elevation myocardial infarction who underwent primary PCI and took a high dose of rosuvastatin didn't have reduced infarct volume by magnetic resonance imaging compared to the low dose rosuvastatin group (17). It has been reported that patients treated with primary PCI who took rosuvastatin showed a significantly lower incidence of non-sustain ventricular tachycardia (18).

Yun et al. studied cardiac biomarker changes (creatinine kinase-MB (CK-MB) and cardiac troponin T) in patients with acute coronary syndrome undergoing PCI. They showed that patients treated with 40 mg rosuvastatin loading dose before PCI had a significantly lower increase in markers and lower cardiac injury, compared to no statin treatment before the procedure group (19).

Our study showed that a loading dose of rosuvastatin before primary PCI was associated with better results. As mentioned above, the results of different studies about the efficacy of rosuvastatin in acute coronary syndrome are different and further studies with a larger sample size could give more exact results.

5.1. Study Limitations

The small sample size of our study restricted sub-group analysis. Further studies with larger sample sizes are needed to provide better facts about using rosuvastatin in daily practice. Because we didn't include the left ventricular ejection fraction before PCI for matching two groups, it probably has affected no-reflow incidence in two groups; however, this effect was minimized by randomization.

5.2. Conclusions

This study demonstrated that using a loading dose of rosuvastatin could reduce the no-reflow phenomenon in patients undergoing primary PCI.

Footnotes

Authors' Contribution: Study concept and design: N. K. and N. A.; Acquisition of data: N. K.; Analysis and interpretation of data: R. H.; Drafting of the manuscript: D. K.; Critical revision of the manuscript for important intellectual content: N. K., N. A., and R. H.; Statistical analysis: R. H.; Administrative, technical, and material support study supervision: N. A.

Clinical Trial Registration Code: IRCT20200722048166N1 (https://en.irct.ir/trial/49776).

Conflict of Interests: The authors declare no conflict of interests.

Data Reproducibility: The dataset presented in the study is available on request from the corresponding author during submission or after its publication.

Ethical Approval: This study was approved by the ethics committee of Tabriz University of Medical Sciences. Code number: IR.TBZMED.REC.1400.394 (link: ethics.research.ac.ir/EthicsProposalView.php?id=212485).

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